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Original Communications

HYDRAULIC FORMULA FOR CALCULATION OF THE AREA OF THE STENOTIC MITRAL VALVE, OTHER CARDIAC VALVES, AND CENTRAL CIRCULATORY SHUNTS. I.

R. GORLIN, M.D.,* AND S. G. GORLIN, M.E.

BOSTON, MASS.

A HITHERTO unsettled problem of the pathologic physiology of the circulation has been the in vivo estimation of degrees of valvular stenosis. Because of the essentially fixed nature of the rings of the cardiac valves when diseased, an attempt has been made to apply the hydraulic principles and formulas of fixed orifices to these stenotic valves.[1] From this approach has come not only a method for gauging valve size but also a better understanding of the unique pressure-flow relationships which obtain across stenotic valves. The methods, in turn, have been applied in estimating the size of three types of central circulatory shunts of congenital origin.

DERIVATION OF THE GENERAL HYDRAULIC ORIFICE FORMULA

In hydraulic systems certain formulas have been developed for fixed orifices.[2] It was decided, after examination of autopsy specimens, that the configuration of the diseased heart valve was most similar to the so-called "rounded-edge" orifice, or short tube. The formula may be derived as follows from two accepted equations:

$$1.\quad F = c_c\, A\, V$$

whereby with a fixed orifice, A, changes in flow, F, are associated with proportionate changes in velocity, V. c_c is the coefficient of orifice contraction. This coefficient allows for the fact that through any except a perfect orifice there will be a contraction of the issuing stream such that the area of the stream will be some fraction less than that of the orifice itself.

From the Medical Clinic, Peter Bent Brigham Hospital, and the Department of Medicine, Harvard Medical School, Boston.

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*United States Public Health Service Research Fellow of the National Heart Institute.

$$2.\quad V^2 = c_v^2\ 2gh \quad or \quad V = c_v\sqrt{2gh}$$

whereby changes in velocity, V, through the orifice are proportional to the square root of the pressure in height, h, of a given liquid standing above the orifice in question. Thus, pressure in height of a given liquid above a given orifice is converted to velocity through that orifice. g is gravity acceleration and in the centimeter-gram-second system equals 980 cm. per second per second. c_v is the coefficient of velocity whereby only a certain fraction of pressure is converted to velocity. The rest is dissipated as frictional losses, turbulence, and so forth.

These two formulas are then combined, and the resulting equation is solved for A:

$$3.\quad A = \frac{F}{c_c \cdot c_v\sqrt{2gh}} \quad or \quad \frac{F}{C \cdot 44.5\sqrt{P_1 - P_2}}$$

F = flow rate through the orifice
C = discharge coefficient (empirical constant)
$44.5 = \sqrt{2g} = \sqrt{1960}$
$P_1 - P_2 = h =$ pressure gradient across the orifice.

In its general form, F is the rate of blood flow during the time the valve or orifice is open; h is the "loss of head" or the pressure gradient across the valve or orifice. For our purposes, the coefficients c_c and c_v have been included in coefficient C which also consists of corrections for the conversion of pressure in millimeters of mercury to centimeters of water and, in the case of the mitral valve, a correction for the method used of estimating the diastolic filling period. The C factor for each particular valve or orifice may be derived empirically; this is best done by comparison of the calculated valve areas with the actually measured areas. In order to justify an empirical rather than a theoretical derivation of each coefficient, the following considerations must be made. The unknowns involved in theoretically estimating the empirical constant are probably incalculable in the face of our limited knowledge of the hemodynamics of steady as well as pulsatile blood flow. Usually, the velocities and diameters are such as to encourage the production of turbulence through the orifice. However, its effects on the coefficient C are unpredictable because, while turbulence may increase frictional energy losses and thus lower c_v, it may decrease the vena contracta effect of the orifice and raise c_c because of the production of eddy currents. Evaluation of turbulence of blood as compared to water is further complicated by its two-phase nature whereby the plasma sleeve may be turbulent but the inner core of blood cells laminar.[3] The C factor corrects for certain practical limitations in the method for deriving the true diastolic filling period of the left ventricle, since left ventricular pressures have not been recorded directly. This correction is obviously unnecessary for valvular lesions of the right side of the heart, where direct ventricular tracings are available by catheter for measurement, and for orifices through which flow is continuous although pulsatile.

It is important to point out that related values may be calculated for an orifice without having a fixed value for C. One may calculate the flow-over-

pressure relationship and derive answers which in relation to one another will be usable. These values, of course, may not be the actual size, but they will differ from the actual size in each case only by the C factor; hence, values in a group of patients will have interpretative usefulness if considered in relation to one another. Once the coefficient is settled upon, all answers may be corrected to give the true orifice area.

The equation described is simply an adaptation of the standard hydrokinetic formula for orifices. Its use here is unique in that across stenotic orifices or through short tubes with high volume flow, kinetic energy losses are very high. Pressure is rapidly dissipated in conversion to velocity here, whereas elsewhere pressure losses are due mainly to friction through areas of large wetted perimeters in relation to area with only minor amounts being lost in conversion to velocity. This peculiar difference, albeit a physical one, indicates why Poiseuille's resistance may not be an accurate gauge of stenosis. Resistance depends on the relation of pressure to flow in a steady velocity and flow system where R is inversely dependent, to a large extent, upon the cross-sectional area.

All values entering the equation are reckoned in the centimeter-gram system. Pressures are recorded as millimeters of mercury but are converted to centimeters of water by the number 1.36. Because the square root of pressure is used in the equation, the square root of the conversion factor, 1.17, is incorporated in the C factor. Because the cardiac output by the Fick method is a quantitative measurement of the actual flow,[4] this is used as the mean flow per minute. The time of flow per minute is defined as that portion of the cardiac cycle when blood actually flows across the orifice in question times the pulse rate; this gives the seconds of flow per minute. In the presence of a stenosis, flow probably continues at a more even rate during the time the orifice is open than when the orifice is normal. No correction is made for pulsatile flow. Pulsatile flow probably increases frictional losses of energy through an orifice; any such effects will be corrected for by the empirical C factor.

To confirm the applicability of this formula to the living patient, a fresh autopsy specimen of a stenotic mitral valve was set up in an artificial pressure and flow system. A steady rate of flow of water through the stenotic valve was measured at different heads of pressure. Readings at all levels yielded calculated areas which checked closely with one another and which were plotted as a parabolic curve (Fig. 1), as might be expected from the equation. When a C factor of 0.5 was used, which when multiplied by the square root of 2g equalled 21, the values were all corrected to the measured area. The factor is different from that of the valve in situ because water was used instead of blood, flow was steady instead of pulsatile, and no correction was necessary for pressure units used. Using Henderson's data[5] from a similar experiment, where atrial pressure was 15 cm. of water and flow rate 52 c.c. per second, an area of 0.5 cm.^{2} could be calculated which compared favorably to the actual area of 0.4 to 0.6 cm.^{2} Although there was ample theoretical evidence, this experimental evidence indicated the applicability of the orifice formula to the calculation of the size of stenotic valves.

METHODS

On the day of study, the patients fasted or else received a light breakfast of orange juice, toast, jam, and black coffee. Cardiac catheterization was performed in the usual fashion. Pulmonary "capillary" pressure[6] was recorded at rest (after five minutes or more, during which time pulse and respiration had become stable) and in some of the studies again during exercise (at the second minute of a three-minute period of exercise as described later). Sufficient time was allowed between exercise periods to allow pulse and respiration to return to normal—usually ten minutes or more.

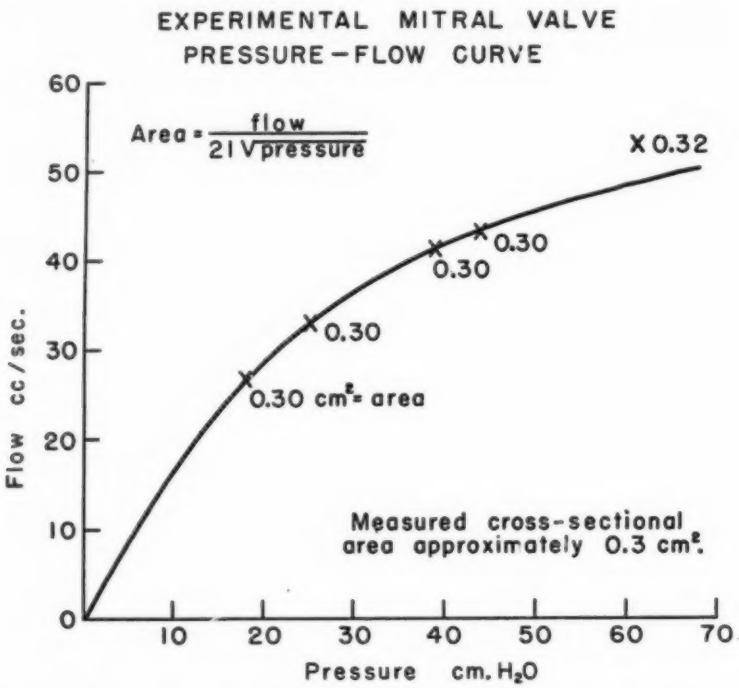

Fig. 1.—A parabolic curve is plotted from actual pressures and flows measured through a stenotic mitral valve set up in an artificial system. The uniformity of values for the calculated areas of the mitral valve orifice at different flows and pressures indicates the applicability of the orifice formula to the calculation of the size of stenotic valve orifices.

The catheter was then withdrawn to a point just distal to the bifurcation of the pulmonary artery. A No. 20 or 21 short-bevel needle was inserted into the brachial artery, the lumen of which was kept patent by a slow intravenous saline solution infusion. After pulse and respiration had returned to the initial resting level, a resting cardiac output was measured by the direct Fick method. Expired air was collected for three minutes in a Douglas bag, and blood samples were withdrawn simultaneously from the brachial artery and pulmonary artery midway during the gas collection. Immediately thereafter, pressures in the pulmonary and brachial arteries were recorded. In those patients who were exercised, pressures were taken after two minutes of exercise. Expired air was

collected between 2.5 and 3.0 minutes. Midway during the collection of the expired air, blood samples were withdrawn from the pulmonary and systemic arteries simultaneously. The volume of expired air was measured in a Tissot spirometer, and the concentration of oxygen alone was measured by a Pauling oxygen analyzer. From previous studies[7] of the Haldane analysis of expired air, mean correction factors of 1.007 and 1.01 were derived for converting expired volume to inspired volume under resting conditions and during exercise, respectively. Blood samples were analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill[8] and the arteriovenous oxygen difference was calculated.

Pressures were measured with Hamilton manometers[9] or, in the latter part of the series, with electromanometers*[10] which recorded on a multi-channel, direct-writing oscillograph. The recording was calibrated with a mercury manometer after each pressure tracing. The zero point for all pressures was 10 cm. anterior to the back with the patient recumbent. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by planimetric integration of the pressure tracings when the Hamilton manometer was used and by electrical integration when the oscillographic tracings were used.

Exercise was performed with the patient recumbent, pedalling a bicycle at the rate of 56 r.p.m., timed with a metronome.

THE MITRAL VALVE

The formula for calculation of the cross-sectional area of the mitral valve was as follows:

$$MVA = \frac{MVF}{31\sqrt{\text{"PC"} - 5}}$$

where MVA = mitral valve area in cm.^{2}

$$MVF = \text{mitral valve flow in c.c. per second} \left(\frac{\text{cardiac output in c.c. per minute}}{\text{diastolic filling period in seconds per minute}} \right)$$

"PC" = pulmonary "capillary" pressure in mm. Hg

5 = left ventricular diastolic pressure in mm. Hg, assumed

$31 = C\sqrt{2g} = 0.7\sqrt{1960}$.

The factors entering into this equation as applied to the mitral valve are as follows:

Mitral Valve Flow (MVF).—Cardiac output is measured in cubic centimeters per minute. Blood actually flows through the mitral valve, however, only during part of each cardiac cycle, namely ventricular diastole. The duration in seconds of this diastolic period, multiplied by the pulse rate, gives the number of seconds per minute during which blood actually flows through the valve. In the presence of any degree of mitral stenosis, blood probably flows through the valve during the entire period of ventricular diastole.[11] This period is called the

*Sanborn Company, Cambridge, Mass.

diastolic filling period. Cardiac output divided by diastolic filling period per minute gives the rate of flow through the valve.

The actual period of diastolic filling can best be obtained by measurement on a left ventricular pressure tracing. The technique of catheterization of the left ventricle has not been used in this laboratory. Instead, we have calculated total diastole from the brachial arterial tracing. The period of diastole per beat was measured from the beginning of the dicrotic notch to the beginning of the upstroke of the next pressure pulse (Fig. 2). As seen in Fig. 3,*A*, values

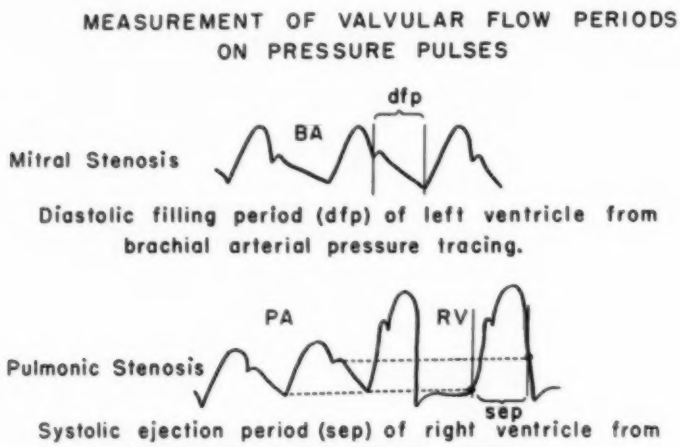

Fig. 2.—On the above drawings from actual pressure tracings are marked the periods of diastolic filling and systolic ejection for the mitral, pulmonic, and tricuspid valves. *BA* = brachial artery; *PA* = pulmonary artery; *RV* = right ventricle; RA_m = right atrial mean pressure.

for our normal patients were compared to a curve derived from Lombard and Cope's[12,13] theoretical formula for calculation of ventricular systole with the subject in the recumbent position. Although their curve really was applicable only to carotid artery measurement, we nevertheless compared our brachial arterial values from twelve normal individuals with their curve. Our values for ventricular diastole described a curve similar in contour and of slightly lesser values than theirs. The average difference between our normal curve and theirs was −0.03 second. Because of the similarity of the two curves and because of the small standard error of the Lombard-Cope method (0.025 second), it was believed that the use of the brachial artery would give sufficiently consistent results for our purposes.

This measurement gives the period of total diastole and, as opposed to measurement of diastole on a ventricular pressure curve, includes the phases of isometric contraction and relaxation. Ordinarily, atrioventricular flow or true diastolic filling does not take place during these phases. Hence, estimation by this technique ordinarily yields a longer duration of the period of ventricular inflow than really exists. In the presence of mitral stenosis, however, because the high atrial pressures maintain a pressure gradient longer than normally, flow probably begins during isometric relaxation, when ventricular pressures fall below atrial pressures, and probably ends during isometric contraction, when pressure finally rises above the high atrial pressure. Three considerations in calculating diastolic filling have been mentioned, two of which are opposed to the third in their effect in estimating this period. Diastole measured from a carotid arterial tracing gives a longer period of filling than ordinarily occurs.

DURATION OF LEFT VENTRICULAR DIASTOLE MEASURED INDIRECTLY IN MAN

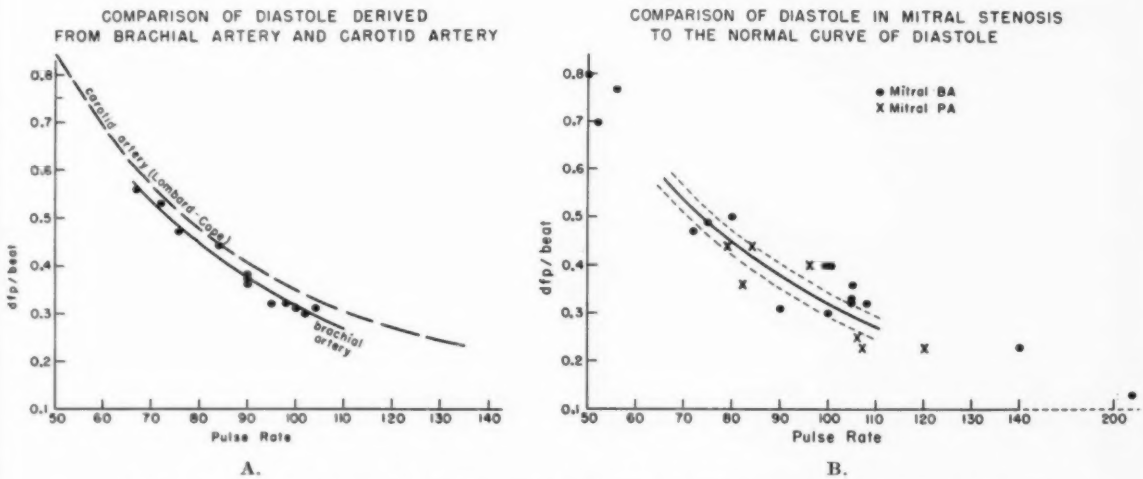

Fig. 3.—*A*, In the graph on the left, normal values for the duration of left ventricular diastole taken from brachial arterial tracings are plotted, making a curve similar in contour to that of Lombard and Cope.[12,13]

***B*, In the graph on the right is drawn the normal curve for left ventricular diastole obtained from brachial arterial tracings, with the dotted lines representing the normal variation. The values for diastole in patients with mitral stenosis are plotted in relation to this curve. Most values were taken from the brachial artery (dot), while a few were measured on pulmonary arterial tracings (x).**

The brachial arterial values used here have been consistently less than those in the carotid artery (−0.03 second) and, hence, closer to the true filling period. In mitral stenosis, atrioventricular flow probably encroaches upon part of the isometric periods of contraction and relaxation, so that flow probably continues longer than during normal diastole. The magnitude of these errors in measuring true diastolic filling period cannot be estimated accurately without analysis of left ventricular tracings. Based on the work of Wiggers and Clough[14] and Burstein[15] for the estimation of the duration of isometric phases of contraction and relaxation, the error probably does not exceed ±10 per cent of any value

derived by this method. In fact, if atrioventricular flow persists during only one-third of the isometric phases (0.04 to 0.05 second), then under most conditions true diastole is not more than 0.05 second less than the estimated diastolic period from the brachial artery tracing. It was decided to effect final adjustment of these errors by modifying the C factor.

In the presence of mitral stenosis, appraisal of abnormalities of the duration of diastole is difficult. Whether deviations from the normal are due to slight errors of the method or to actual ventricular dysfunction with prolonged systole is not always clear. In some cases, where no peripheral arterial pressures were recorded, pulmonary arterial tracings were measured and utilized (Fig. 3,*B*). Because of the usual right ventricular strain seen in mitral stenosis, the duration of right ventricular systole was sometimes longer than the left, the result being in those instances that we may have used a slightly shorter period for left ventricular diastolic filling than probably actually occurred. That the variation was not striking, however, is seen if one examines Fig. 3,*B*, where the pulmonary arterial measurements are shown by an *x*.

Pressure Gradient Across the Mitral Valve ($P_1 - P_2$ or "PC" − 5).—For the mitral valve, P_1 is left atrial mean and P_2 left ventricular mean diastolic pressure. Studies in dogs and in human beings with atrial septal defect have indicated that pulmonary "capillary" pressure, as measured, is within a few millimeters of mercury of left atrial pressure.[16] Therefore, pulmonary "capillary" pressure ("PC") may be used here as an index of left atrial pressure or P_1. P_2 cannot be measured directly by right heart catheterization techniques. Reports of Zimmerman[17] on the left ventricular diastolic pressure of normal individuals and our own studies of patients with atrial septal defect[18] who had cardiac indices similar to the patients with mitral stenosis have indicated that left ventricular mean diastolic pressure is probably about 5 mm. Hg. Because this value for the left ventricular diastolic pressure is usually subtracted from a much larger number (pulmonary "capillary" pressure) and the square root of the subtraction is finally utilized in the equation, an error of ±100 per cent in the ventricular diastolic pressure will not materially affect the validity of estimation of the gradient. For example, with a pulmonary "capillary" pressure of 30 mm. Hg, subtracting 0, 5, or 10 mm. Hg and obtaining the square root will yield 5.5, 5, or 4.5 as the factor in the denominator of the area equation. It naturally follows that the lower the pulmonary "capillary" pressure and the less the gradient, the more inaccurate the calculation of valve area. Under these circumstances, it is advisable to alter the circulatory dynamics so as to elevate pulmonary "capillary" pressure. This has been accomplished in this laboratory by the use of a three-minute period of exercise as described elsewhere.[7]

The major factor which might materially alter the actual left ventricular diastolic pressure in pure mitral stenosis would be active rheumatic myocarditis. Bland and Sweet[19] pointed out, however, that in most cases of predominantly mitral stenosis the myocardium itself was actually "too good." Walsh and associates[20] believed that patients with pure mitral stenosis had a singularly mild type of rheumatic fever without frequent recurrence. In general, most of the patients presented in this study had predominantly pure mitral stenosis,

and only one had symptoms to suggest active rheumatism at the time of the study. That diastolic pressures up to 10 mm. Hg in the left ventricle will not materially affect the calculation (see preceding paragraph) tends to minimize the error of all but the most severe effects of myocardial insufficiency.

Empirical Constant.—This factor corrects for (1) anomalies of discharge through an orifice, (2) errors in calculating diastolic filling period, as already discussed, and (3) the conversion of millimeters of mercury to centimeters of water (1.17). By comparison of the valve area measured in the first patient with mitral stenosis at autopsy with the calculated area, a value of 0.7 was derived for C. Subsequent autopsy material confirmed the use of this value for C.

Methods of Measurement.—Cardiac output as measured by the direct Fick method was utilized in the calculation of mitral valve blood flow. In the presence of valvular regurgitation where a significant fraction of the stroke output is not discharged forward, the Fick method will not record the true cardiac minute volume but only the forward or effective minute volume. Of necessity, then, rates of flow as calculated from the Fick output in the presence of regurgitation will be much lower than are actually occurring through the orifice, and the valve area, as calculated, will be correspondingly smaller. This valve estimate is called the "effective valve area." Regurgitation can be detected by pulmonary "capillary" wave form or pulse pressure,[21] if not clinically, and appropriate reservation made of the accuracy of the calculated size of the stenotic orifice in its presence.

Pulse rate was measured directly on the pressure tracing at the time of cardiac output.

In the studies with the patients at rest, pressure was measured in the pulmonary "capillaries." The catheter was immediately withdrawn to the bifurcation of the pulmonary artery and a cardiac output and pressure tracing obtained. Delay was kept to a minimum.

Results.—Observations have been made on twenty-one patients with mitral stenosis (Table I).[22,23] The data gathered from six patients at autopsy and from five patients at operation are presented in Table II. Areas were measured at autopsy by standard gross techniques and at operation by intracardiac digital palpation.* The C factor was derived by adjusting the values obtained from the formula to the measured area in one patient; subsequent comparisons between calculated and measured areas showed close agreement, using this C factor. Values varying from 0.4 to 2.5 cm.^{2} have been calculated.[22] A typical calculation is as follows:

Patient R. C.:

Cardiac output = 5,300 c.c. per minute
Diastolic filling period per beat = 0.31 second per beat
Pulse rate = 108
Diastolic filling period per minute = 34 seconds per minute
Pulmonary "capillary" pressure = 39 mm. Hg
Left ventricular mean diastolic pressure (assumed) = 5 mm. Hg

*By Dr. Dwight E. Harken, Boston, Mass.

TABLE I. DATA RELATIVE TO CALCULATION OF VALVE AREA IN MITRAL STENOSIS

PATIENT	STATE	DIASTOLIC FILLING PERIOD (SECOND PER BEAT)	PULSE RATE (PER MINUTE)	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	MITRAL VALVULAR FLOW (C.C. PER SECOND)	PULMONARY "CAPILLARY" PRESSURE (MM. Hg)	MITRAL VALVE AREA (CM.^{2})
J. D.	Rest	0.31	100	31	9.4	303	19	2.6
	Exercise	0.22	120	27	11.1	411	41	2.2
J. F.	Rest	0.47	72	34	6.5	192	21	1.6
	Exercise	0.25	110	28	9.4	330	46	1.6
L. B.	Rest	0.31	90	28	4.8	172	20	1.4
J. M.	Rest	0.23‡	107	25	4.4§	176	25	1.3
L. C.	Rest	0.25‡	106	27	5.4	200	27	1.4
Gr.*	Rest	0.40	100	40	7.0	175	32	1.1
	Rest	0.23‡	120	27	4.7§	175	38	1.0
Ba.	Rest	0.33	105	35	5.2	148	32	0.9
Ba.†	Rest	0.32	100	32	5.5	172	19	1.5
	Exercise	0.16	142	23	5.9	256	30	1.7
	Recovery	0.32	100	32	5.6	175	20	1.5
L. T.	Rest	0.52	70	36	4.4	122	24	0.9
	Exercise	0.30	108	32	5.7	178	46	0.9
	Recovery	0.48	76	36	3.9	109	26	0.8
R. C.	Rest	0.31	108	34	5.3	156	39	0.9
M. B.	Rest	0.40	96	38	3.2	84	17	0.8
	Exercise	0.41	93	38	4.8	126	28	0.9
M. T.	Rest	0.44‡	79	35	3.2	91	21	0.7
E. S.*	Rest	0.50	80	40	3.9	98	26	0.7
	Exercise	0.30	94	28	4.1	145	51	0.7
	Rest	0.44	84	37	3.3	89	28	0.6
	Exercise	0.48	70	33	4.1	124	35	0.7
E. D.	Rest	0.23	140	32	3.5	109	36	0.6
C. M.	Rest	0.34	94	32	3.1	97	29	0.6
N. L.	Rest	0.36	105	38	3.2	84	28	0.5
	Exercise	0.24	136	33	4.0	120	35	0.7
M. G.	Rest	0.36‡	82	30	2.7§	90	30	0.6
Mc. L.	Rest	0.32	105	33	4.2	127	54	0.6
R. W.	Rest	0.49	75	37	3.5	95	34	0.6
	Exercise		120		4.0		47	
R. W.†	Rest	0.52	71	37	2.9	78	11	1.1
	Exercise	0.48	75	36	3.5	97	13	1.2
D. K.	Rest	0.13	204	26	2.5§	96	46	0.5

TABLE I.—CONTD.

PATIENT	STATE	DIASTOLIC FILLING PERIOD (SECOND PER BEAT)	PULSE RATE (PER MINUTE)	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	MITRAL VALVULAR FLOW (C.C. PER SECOND)	PULMONARY "CAPILLARY" PRESSURE (MM. Hg)	MITRAL VALVE AREA (CM.²)
W. F.	Rest	0.50	80	40	2.6	65	23	0.5
M. M.	Rest	0.77	56	43	2.3	54	22	0.4
	Exercise	0.25	136	34	2.8	82	35	0.5
	Recovery	0.76	56	43	2.5	58	25	0.4
D. V.	Rest	0.40	100	40	3.0	75	35	0.4

*Data were obtained from two separate catheterizations.
†Study was done three weeks after mitral valvuloplasty.
‡Measured on pulmonary arterial tracing.
§Benedict-Roth method used for oxygen consumption.

1. Mitral valvular rate of flow (MVF)

$$MVF = \frac{\text{cardiac output}}{\text{diastolic filling period per minute}} = \frac{5{,}300 \text{ c.c. per minute}}{34 \text{ seconds per minute}} = 156 \text{ c.c. per second}$$

2. Mitral valvular pressure gradient = "PC" − 5 = 39 − 5 = 34 mm. Hg

3. Mitral valve area $= \frac{156}{31\sqrt{34}} = 0.9$ cm.²

TABLE II. COMPARISON OF CALCULATED AND MEASURED MITRAL VALVE CROSS-SECTIONAL AREAS

PATIENT	MITRAL VALVE AREA (CM.²)		
	CALCULATED	MEASURED	
		AUTOPSY	OPERATION
L. C.	1.4	1.3–1.5	
M. T.	0.8	0.5–0.7	
N. L.	0.6	0.5–0.6	
M. G.	0.6	0.6–0.8	
C. M.	(0.6)*	0.7–0.8	
M. M.	0.4	0.5–0.6	
E. D.	0.6		0.5
R. W.	0.6		0.5
Ba.	0.9		1.1
W. F.	0.6		0.5
Gr.	1.1		0.9
	1.0		

*This figure is based on a theoretical diastolic filling period for the pulse rate observed (see Fig. 2) because simultaneous brachial arterial pressure tracing was not obtained.

In two patients (Gr. and E. S.) calculations of area from data of repeated catheterizations (Table III) were made which checked within 0.1 cm.^{2} Values at rest, during exercise, and upon recovery in ten instances (Table III) likewise checked in nine patients within 0.2 cm.^{2} and within 0.4 cm.^{2} in the tenth. This indicates the reproducibility of results under varying conditions and probably indicates no significant change in valve size on exercise. Evidence that this method may make it possible to detect a change in valve size is afforded in two patients (Table IV) whose valves were enlarged by finger fracture valvuloplasty. The preoperative areas were calculated to be 0.6 and 0.9 cm.^{2}, respectively, and postoperatively averaged 1.2 and 1.6 cm.^{2}, respectively.

TABLE III. REPEATED CALCULATION OF MITRAL VALVE AREA FROM MULTIPLE SETS OF DATA AS AN INDEX OF ACCURACY OF THE METHOD

PATIENT	MITRAL VALVE AREA (CM.^{2})		
	RESTING	EXERCISE	RECOVERY
Gr.*	1.1		
	1.0		
E. S.*	0.7	0.7	
	0.6	0.7	
J. D.	2.6	2.2	
J. F.	1.6	1.6	
N. L.	0.6	0.7	
M. B.	0.8	0.9	
M. M.	0.4	0.5	0.4
L. Y.	0.9	0.9	0.8
R. W.	1.1	1.2	
Ba.	1.5	1.7	1.5

*Two separate cardiac catheterizations were performed.

TABLE IV. CALCULATION OF MITRAL VALVE AREA BEFORE AND AFTER MITRAL VALVULOPLASTY TO INDICATE ABILITY OF METHOD TO DETECT CHANGES IN VALVE SIZE

PATIENT	MITRAL VALVULOPLASTY	MITRAL VALVE AREA (CM.^{2})		
		RESTING	EXERCISE	RECOVERY
R. W.	Preoperative	0.6		
	Postoperative	1.1	1.2	
Ba.	Preoperative	0.9		
	Postoperative	1.5	1.7	1.5

In Table V is seen the relation of cross-sectional valve area to the clinical functional classification[24] of the twenty-one patients with mitral stenosis. Patients whose valvular areas were 2.5 cm.^{2} or greater had no symptoms of pulmonary congestion. Those whose areas were between 1.5 and 2.5 cm.^{2} had only mild symptoms, while patients with areas less than 1 cm.^{2} invariably were severely limited. In occasional individuals, as in Patient L. C.,[22] the symptoms may not

necessarily be related to valve area if the symptoms are due to complicating pulmonary vascular disease or myocardial failure.

TABLE V. RELATION OF VALVULAR CROSS-SECTIONAL AREA TO CLINICAL SYMPTOMS IN PATIENTS WITH MITRAL STENOSIS

CLINICAL CLASSIFICATION	MITRAL VALVE AREA (CM.^{2})	NO. PATIENTS	PHYSICAL ACTIVITY
I	2.5	1	Virtually unlimited
II	1.3–1.6	3	Some limitations
III	0.6–1.1	4	Very limited
IV	0.4–0.9	12*	Bed and chair

*One patient with proved valve area of 1.4 cm.^{2} is excluded because symptoms were due to severe pulmonary vascular disease.

The reason for the relationship of pulmonary symptoms to mitral valve area becomes apparent from Fig. 4. Because pressure varies inversely as the square of the area, below a critical cross-sectional area of about 1 cm.^{2}, the pressure gradient required for a blood flow compatible with life must become inordinately high. The slow decrease in valve area due to chronic cicatricial contraction may at some critical point suddenly begin to produce symptoms as pulmonary pressures rise sharply to high levels in order to maintain flow.

Discussion.—The practical applications of the formula are manifold. Perhaps its greatest use has been in the objective appraisal of operative procedures on the mitral valve,[25] wherein definite increases in valve area following operation may be detected. Determination of area may be of aid in the selection of complicated cases for valve surgery. Use of theoretical pressure-flow curves plotted from this formula (Fig. 4) has indicated the size of the valve orifice that must be created at operation in order to relieve symptoms satisfactorily and to rehabilitate patients with mitral stenosis. That flows of 200 to 400 c.c. per diastolic second through the mitral valve (equivalent to a cardiac output of 7 to 15 liters per minute at a pulse rate of 80 or 5 to 10 liters per minute at a pulse rate of 120) may be tolerated when the valve area is 2.5 cm.^{2} or above would make this the goal for the cardiac surgeon to aim for. The lack of major symptoms in patients with valve areas greater than 1.5 cm.^{2} would suggest that operative procedures on the mitral valve should be considered only in those patients with mitral stenosis who have symptoms which can be directly attributed to a valve area of less than 1.5 cm.^{2}

By means of the formula, an analysis may be made of those other factors which influence the pulmonary "capillary" pressure in mitral stenosis by solving the formula for "PC." Thus, the factors responsible for pulmonary edema in this disease may be clarified.[26]

In the normal patient, most of the flow occurs within the first tenth of a second of diastole and during atrial systole because of the large valve area. Because valvular flow may cease between these two periods, there will be great variations in flow rate through the valve. Although there must be some pressure loss through the orifice, no detectable gradient has been recorded as yet. Using

a mean rate of flow through a valve orifice of normal size (4 to 6 cm.^{2}), a theoretical mean pressure gradient may be calculated. Inability to measure the pressure gradient across the normal valve precludes any accurate physiologic measurement of the normal valve area.

THE PULMONIC VALVE

The formula derived for calculation of the cross-sectional area of the pulmonic valve was as follows:

$$PVA = \frac{PVF}{44.5\sqrt{RV_{sm} - PA_{sm}}}$$

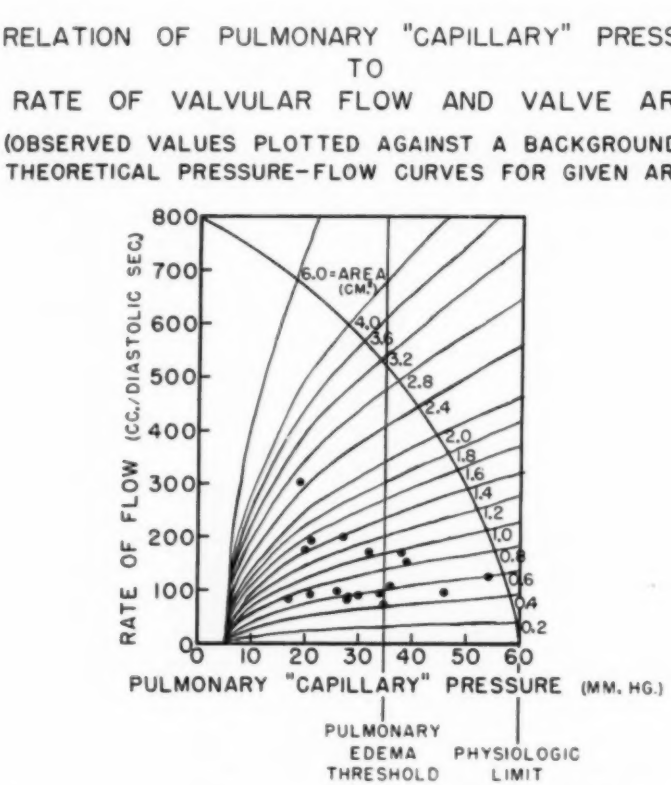

Fig. 4.—This shows theoretical pressure and flow curves for different mitral valve cross-sectional areas. The vertical line at 35 mm. Hg indicates an arbitrary pressure threshold above which most patients develop symptoms of pulmonary congestion. Life can be maintained at mitral valve flow rates as low as 50 c.c. per second if the pulse rate is slow. It is seen that at the smaller valve areas, great changes must occur in pulmonary "capillary" pressure for small changes in valvular flow.

Six patients, all with severe mitral stenosis, were in gross pulmonary edema at the time of the study (pressure above 35 mm. Hg). The pressure elevation was related entirely to the rate of valvular flow at the time. Normal individuals in whom the mitral valve orifice is 4 to 6 cm.^{2} have a large reserve and do not develop pulmonary edema even with huge rates of flow such as occur under the most severe exertion (as much as 700 c.c. per second). Patients with mild mitral stenosis (2.5 cm.^{2}) can tolerate flows up to 400 c.c. per second before pulmonary "capillary" pressure exceeds 35 mm. Hg. As a result, they can easily perform ordinary exertions. Flow rates up to 250 c.c. per second can be handled by patients whose valve orifice area is 1.5 cm.^{2} These patients usually have no symptoms at rest or on mild activity. In patients with severe mitral stenosis (1 cm.^{2} or less), rates of flow above 150 c.c. per second will easily produce pulmonary edema.

where PVA = pulmonic valve area in cm.^{2}
PVF = pulmonic valve flow in c.c. per second $\left(\frac{\text{cardiac output}}{\text{systolic ejection period, seconds per minute}}\right)$

RV_{sm} = right ventricular mean systolic ejection pressure in mm. Hg
PA_{sm} = pulmonary arterial mean systolic pressure in mm. Hg
$44.5 = C\sqrt{2g} = 1.0\sqrt{1960.}$

Pulmonic Valvular Flow (PVF).—The flow rate across this valve is obtained by dividing the cardiac output by the time during which blood actually flows through the valve per minute. Here flow occurs only during ventricular systole. Systole in seconds may be measured directly on the right ventricular tracing from the point where the right ventricular pressure equals pulmonary arterial diastolic pressure to the point where right ventricular pressure equals the pulmonary arterial dicrotic notch (Fig. 2). This is the period of systolic ejection per beat and, if multiplied by the pulse, gives the systolic ejection period (SEP) in seconds per minute. Thus, the actual rate of flow through the pulmonic valve may be derived by dividing the cardiac output per minute by the systolic ejection period per minute.

Pressure Gradient Across the Pulmonic Valve ($P_1 - P_2$ or $RV_{sm} - PA_{sm}$).—P_1 is the right ventricular systolic ejection mean pressure (RV_{sm}); P_2 is the pulmonary arterial systolic mean pressure (PA_{sm}). P_1 may be calculated directly on the pressure tracing by planimetric integration of the area during systolic ejection from the point where right ventricular pressure equals pulmonary arterial diastolic pressure to the point where pressure equals that at the dicrotic notch of the pulmonary arterial pressure tracing. This area is divided by the duration of systole to give the right ventricular mean pressure during systolic ejection. Pulmonary arterial mean systolic pressure in most patients with pulmonic stenosis is almost the same as pulmonary arterial mean pressure due to the small and unsustained systolic component in the pulmonary circuit. Hence, an electrically integrated mean pressure may be utilized. In patients with mild pulmonic stenosis, however, utilization of the pulmonary arterial mean pressure may introduce considerable error, and in these patients the systolic mean pressure should be measured. The area under the pulmonary arterial curve, from the beginning of the systolic upstroke to the dicrotic notch, is planimetrically integrated to give this pressure.

Empirical Constant.—At present a value of 1.0 is being used for C. Because the mercury conversion factor of 1.17 is included in C, the actual "discharge" coefficient ($c_v \cdot c_c$) of the orifice is 0.85.

Methods.—Transvalvular pressures were recorded in consecutive fashion immediately following the determination of cardiac output in studies on ten patients at rest. In one other patient, studied at rest, blood sampling and pressures were performed in immediate consecutive order, while oxygen consumption was determined by the Benedict-Roth method just before catheterization. Simultaneous cardiac outputs, pulmonary artery and right ventricular pressures were recorded in the single rest-exercise study by means of a double-lumen catheter.

Results.—Observations have been made in twelve cases of pulmonic stenosis. Only one of these patients subsequently came to autopsy. Direct comparison of calculated and measured areas in this case indicated a C factor of 1.0. That this C factor is higher than that for the mitral valve is due, in part, to the fact that here a true period of blood flow may be directly measured from the ventricular pressure tracings and is due possibly to different anatomic characteristics of the pulmonic valve orifice with respect to orifice contraction and turbulence and to the generally higher pressure gradients. In Table VI are presented the pulmonic valve areas in twelve patients with pulmonic stenosis, eight of whom were previously reported from this laboratory.[27] The definition of the value for C must await further comparison of physiologic and autopsy findings. Also in Table VI are the pulmonic stenosis resistances, calculated as described elsewhere.[27] Although the number derived is only an index of resistance, there seems to be an inverse directional correlation between the degree of anatomic stenosis in $cm.^2$ and the degree of resistance in dynes seconds $cm.^{-5}$

TABLE VI. DATA RELATIVE TO CALCULATION OF VALVE AREA IN CONGENITAL PULMONIC STENOSIS

PATIENT	SYSTOLIC EJECTION PERIOD (SECOND PER BEAT)	PULSE RATE	SYSTOLIC EJECTION PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	PULMONIC VALVE FLOW (C.C. PER SECOND)	PRESSURES (MM. Hg)		PULMONIC VALVE AREA ($CM.^2$)	PULMONIC VALVE RESISTANCE (DYNES SECOND $CM.^{-5}$)
						RIGHT VENTRICULAR MEAN SYSTOLIC EJECTION	PULMONARY ARTERIAL MEAN SYSTOLIC		
S. C.	0.32	69	22	4.6	209	19	15	2.3	69
W. H.	0.35	71	25	5.8	232	26	21	2.3	69
A. J.	0.38	60	23	5.0	217	56	15	0.8	656
R. L.	0.26	150	39	6.9	177	63	20	0.6	498
T. M.	0.21	114	24	5.6	233	35	22	1.5	186
J. M.	0.31	80	25	3.1	124	30	19	0.9	284
W. P.	0.36	72	26	7.2	277	30	21	2.1	99
E. R.	0.31	70	22	5.3	241	24	17	2.0	106
M. L.	0.26	110	29	8.5	293	78	13*	0.8	620
P. B.	0.32	88	28	2.2	79	63	8*	0.2 0.2†	2000
D. H.	0.35	71	25	4.6	184	66	10*	0.6	974
W. E. (Rest)	0.32	90	29	8.7	300	51	11*	1.1	456
W. E. (Exercise)	0.26	120	31	11.9	384	64	17*	1.2	376

*Pulmonary arterial mean pressure.
†Valve area measured at autopsy.

Discussion.—There are two reasons for calculating the valvular area. One may better prognosticate on the clinical course in pulmonic stenosis with a proper evaluation of the orifice stenosis against which the ventricle works. Second, it is becoming feasible to widen the stenotic pulmonic orifice surgically and, as in the case of mitral stenosis, theoretical planning and interpretation of the results of operation will be enhanced by the use of the orifice formula.

THE TRICUSPID VALVE

The formula derived for the cross-sectional area of the tricuspid valve was:

$$TVA = \frac{TVF}{44.5\sqrt{RA_m - RV_{md}}}$$

where TVA = tricuspid valve area in cm.^{2}

TVF = tricuspid valve flow in c.c. per second $\left(\frac{\text{cardiac output}}{\text{diastolic filling period per minute}}\right)$

RA_m = right atrial mean pressure in mm. Hg

RV_{md} = right ventricular mean diastolic pressure in mm. Hg

$44.5 = C\sqrt{2g} = 1.0\sqrt{1960}$.

Tricuspid Valvular Flow (TVF).—The flow rate across this valve is obtained by dividing the cardiac output by the right ventricular diastolic filling period per minute. This period per beat is measured directly on the right ventricular pressure tracing from the point on the downstroke of the ventricular complex where the pressure equals right atrial mean pressure to the point on the upstroke of the next complex where right ventricular pressure again equals right atrial mean pressure (Fig. 2). This period is multiplied by the pulse rate to give the diastolic filling period in seconds per minute.

Pressure Gradient Across the Tricuspid Valve ($P_1 - P_2$ or $RA_m - RV_{md}$).—P_1 is right atrial mean pressure. Because of the small differences between atrial mean pressure and the actual atrial pressure during ventricular filling, no attempt was made to correct for the 1 or 2 mm. Hg discrepancy. P_2 is right ventricular mean diastolic pressure rather than the end diastolic pressure.

Empirical Constant.—No value for C has been settled as yet. C is greater than 0.7 because no correction for diastolic filling period is necessary. For the present, we are using the value of 1.0, which implies a "discharge" coefficient ($c_c \cdot c_v$) of 0.85. It should be clearly understood that this number may be changed with the collection of autopsy data.

Methods.—In both instances, pressures were recorded in the right ventricle and atrium by continuous withdrawal of the catheter shortly after measurement of cardiac output with the catheter in the pulmonary artery.

Results.—One case of almost pure tricuspid stenosis has been studied twice in this laboratory. Values of 1.1 and 1.2 cm.^{2} were calculated, using C = 1.0 (Table VII). Due to the rarity of tricuspid stenosis without regurgitation, no other studies have been carried out to date.

This patient was subsequently operated upon, immediately following which the venous pressure fell from 21 to 4 mm. Hg and has stayed at this level to date. A detailed postoperative study of circulatory dynamics for appraisal of tricuspid valvular dynamics was deemed inadvisable because thrombi were observed to be present in the right atrium at operation.

Discussion.—The indications for calculating valve area are the same as for mitral and pulmonic stenosis.

TABLE VII. DATA RELATIVE TO CALCULATION OF VALVE AREA IN TRICUSPID STENOSIS

PATIENT	DIASTOLIC FILLING PERIOD (SECONDS PER BEAT)	PULSE RATE	DIASTOLIC FILLING PERIOD (SECONDS PER MINUTE)	CARDIAC OUTPUT (LITERS PER MINUTE)	TRICUSPID VALVE FLOW (C.C. PER SECOND)	PRESSURES (MM. Hg)		CALCULATED TRICUSPID VALVE AREA ($CM.^2$)
						RIGHT ATRIAL MEAN	RIGHT VENTRICULAR MEAN DIASTOLIC	
A. D.	0.26	90	23	3.8	165	14	4	1.2
A. D.	0.20	120	24	3.1	129	15	8	1.1

THE AORTIC VALVE

The formula derived for calculation of the cross-sectional area of the aortic valve would be as follows:

$$AVA = \frac{AVF}{C \times 44.5\sqrt{LV_{sm} - BA_{sm}}}$$

where AVA = aortic valve area in $cm.^2$

$$AVF = \text{aortic valve flow in c.c. per second} \left(\frac{\text{cardiac output}}{\text{systolic ejection period in seconds per minute}} \right)$$

LV_{sm} = left ventricular systolic ejection mean pressure in mm. Hg
BA_{sm} = brachial arterial systolic mean pressure in mm. Hg
C = empirical constant, to be derived
$44.5 = \sqrt{2g} = \sqrt{1960}$.

Aortic Valvular Flow (AVF).—This may be computed by dividing cardiac output by the period of systolic ejection of the left ventricle. This period can be measured on the left ventricular tracing from the point where the left ventricular pressure equals the arterial diastolic pressure to the point where left ventricular pressure falls below the arterial dicrotic notch. This period of systolic ejection per beat can then be multiplied by the pulse rate to give the period of systolic ejection (SEP) in seconds per minute.

Aortic Valvular Pressure Gradient ($P_1 - P_2$ or $LV_{sm} - BA_{sm}$).—P_1 or left ventricular mean systolic ejection pressure is measured in the same fashion as the right ventricular mean systolic ejection pressure as discussed previously; P_2 or the aortic mean systolic pressure is approximated by the brachial arterial mean systolic pressure. This is measured in the same way as the pulmonary arterial mean systolic pressure described previously. Since the systolic pressures in the right ventricle, aorta, and brachial artery have been shown to be equal as measured in patients with dextroposition of the aorta,[28] it may be inferred that the small losses in actual pressure due to velocity between the aorta and brachial artery are probably recorded as pressure in the brachial artery tracing because the recording needle is end on to the stream.

Discussion.—In the presence of clinical or experimental aortic stenosis, if either left ventricular catheterization or direct ventricular puncture during thoracotomy is performed along with measurement of cardiac output, the formula

may be used to calculate the area of the aortic valve. Since this laboratory has not undertaken either left ventricular catheterization in man or the determination of blood flows under anesthesia, no data have been accumulated. It seemed appropriate, however, to include this section for completeness.

PATENT DUCTUS ARTERIOSUS

Patent ductus arteriosus is a short tube only a few centimeters in length which changes in volume and cross-sectional area with each pressure pulse. Because the particular formulas discussed previously apply only to fixed orifices or fixed short tubes, the magnitude of the changes in the cross-sectional area with pressure must be considered before the formula may be used here. Because the patent ductus arteriosus is arterial tissue, the changes in ductus volume and cross-sectional area with pressure as recorded in the aorta (peripheral artery)

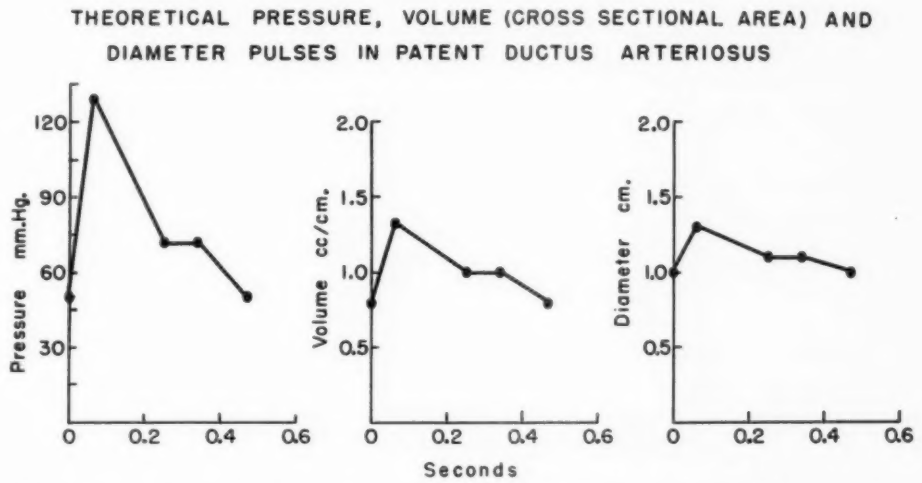

Fig. 5.—The pulses plotted above indicate the changes in cross-sectional area and diameter associated with each pressure pulse in a patent ductus arteriosus of 1 cm. in diameter in diastole. The changes were based on the volume-elasticity curves of Hallock and Benson[29] for human aortas. Note the relatively small change in mean cross-sectional area and diameter during the cardiac cycle.

were reconstructed, utilizing a percentile analysis of the aortic volume changes with pressure from the analysis of Hallock and Benson.[29] While it is true that the volume-elasticity characteristics of a given ductus may be different from the aorta in some patients, this analogy is meant to be only qualitative. In Fig. 5 are seen theoretical pressure-volume pulses for a patent ductus arteriosus of 1 cm. in diameter. Because the volume and cross-sectional area changes induced by pressure changes were not great, it is believed that a mean area can be derived using mean pressures and mean rates of flow.

The formula derived for calculation of the cross-sectional area of the patent ductus arteriosus was as follows:

$$PDAA = \frac{PDAF}{44.5\sqrt{BA_m - PA_m}}$$

where PDAA = patent ductus arteriosus mean area in cm.^{2}
PDAF = patent ductus arteriosus mean flow in c.c. per second
BA_m = brachial arterial mean pressure in mm. Hg
PA_m = pulmonary arterial mean pressure in mm. Hg
$44.5 = C\sqrt{2g} = 1.0\sqrt{1960}$.

Patent Ductus Arteriosus Flow (PDAF).—Flow through the ductus occurs throughout the cardiac cycle, although at a varying rate. Therefore, the mean rate of flow through the ductus is the aortic-pulmonary shunt per second. Patent ductus arteriosus shunt is calculated[30] as the difference between pulmonary and peripheral cardiac outputs.

Patent Ductus Arteriosus Pressure Gradient ($P_1 - P_2$ or $BA_m - PA_m$).—The aortic mean pressure is P_1, and P_2 is the pulmonary arterial mean pressure. Aortic mean pressure is closely approximated by peripheral arterial mean pressure and is the value most conveniently utilized for estimating the gradient.

Empirical Constant.—On the basis of data from operation on two patients, this value has been tentatively found to be 1.0, although it may be altered in the future. Because of the mercury conversion factor of 1.17, the true coefficient of discharge equals 0.85. In a short tube, the contraction coefficient is 1.0, indicating here that the velocity coefficient is 0.85.

Methods.—Data were obtained by cardiac catheterization.* Cardiac outputs were determined by the direct Fick method, and mean pressures were recorded simultaneously in the pulmonary and brachial artery by Hamilton manometers or Sanborn electromanometers.

Pressures were obtained simultaneously with the pulmonary blood flow and shortly before the peripheral blood flow. The method of measuring the pulmonary and peripheral outputs and obtaining the shunt flow through the ductus has been described elsewhere.[30]

Results.—In two patients with patent ductus arteriosus, in whom reliable peripheral and pulmonary arterial pressures and cardiac outputs were determined, the mean areas were calculated to be 2.4 and 1.1 cm.^{2}, respectively, using C equal to 1.0 (Table VIII). With this particular coefficient, the calculated areas of the lumens compared well to external areas of 2.8 and 0.94 cm.^{2}, respectively, calculated from the external diameter of the patent ductus measured at operation before ligation.

Discussion.—Application of this formula to the patent ductus arteriosus admittedly is not strictly accurate because the vessel does change in size with each pressure pulse. This change, however, is not so great (Fig. 5) as to preclude approximating the functional size of a patent ductus. Although pressure, volume, and flow pulses do not follow the same moment-to-moment change with each cardiac cycle,[31] their interrelationship in the large vessels is probably fixed according to the volume elasticity characteristics of the vessel wall. Because

*We are indebted to Dr. J. W. Dow of the Children's Medical Center, Boston, Mass., for one of the studies (I. S.) herein reported.

flow pulses are related to pressure pulse when the elasticity characteristics are fixed, the use of mean pressures and mean flows was considered valid for deriving a mean cross-sectional area. Taylor and associates[32] actually found that shunt flow per 100 c.c. of left ventricular output in most patients was proportional to the square of the radius times the square root of the pressure gradient across the patent ductus. This observed relationship, as they pointed out, is implicit in the orifice or short tube formula.

The area derived by this method is the internal in vivo area or the functional area. It is probable that in some instances, because of a thickened vessel wall, the internal area will be calculated to be considerably less than the external area measured directly at operation. The area so derived from pressure and flow data will be the functioning area which has more physiologic significance than the anatomic external area.

TABLE VIII. DATA RELATIVE TO CALCULATION ON THE CROSS-SECTIONAL AREA OF PATENT DUCTUS ARTERIOSUS

PATIENT	FLOW PERIOD (SECONDS PER MINUTE)	SHUNT OUTPUT (LITERS PER MINUTE)	PATENT DUCTUS ARTERIOSUS FLOW (C.C. PER SECOND)	PRESSURES (MM. Hg)		CALCULATED PATENT DUCTUS ARTERIOSUS AREA ($CM.^2$)	MEASURED PATENT DUCTUS ARTERIOSUS AREA ($CM.^2$)
				BRACHIAL ARTERY MEAN	PULMONARY ARTERY MEAN		
I. S.	60	20	333	80	70	2.4	2.8
F. M. (Rest)	60	21	350	84	37	1.1	0.94
F. M. (Exercise)	60	19.3	320	88	42	1.1	

Thrombosis and recanalization occasionally occur within a ductus. This markedly increases the frictional resistance due to an increase in wetted perimeter in relation to cross-sectional area. The C factor in these instances will be much less than 1.0 because the velocity coefficient will be smaller than 0.85 as used in our patients.

Taylor and associates[32] observed occasional cases where there was not a good correlation between shunt flow and the product of radius squared times the square root of the pressure gradient. This lack of correlation may have been due to either a thickened vessel wall or a tortuous, recanalized channel through the ductus.

The cross-sectional area of most patients with patent ductus arteriosus is greater than 0.5 $cm.^2$ If the area, as calculated, using a C factor of 1.0 (velocity coefficient 0.85) is 0.5 $cm.^2$ or lower, then it is quite probable that the channel through the ductus is narrow or extremely tortuous. Here a discrepancy between expected and calculated area would indicate greater frictional energy losses than were corrected for in the formula.

Although the chance for error is great here, with careful interpretation reasonable estimates may be drawn of the functional size of a patent ductus arteriosus.

ATRIAL SEPTAL DEFECT

The amount of shunting that occurs through an atrial defect depends on the size of the defect and the pressure gradient across it. As has been discussed by Dow and Dexter,[33] the normal interatrial pressure difference depends on the different volume-elasticity characteristics of the two ventricles. As in an orifice submerged in liquid on both sides, flow will continue only as long as there is a difference in pressure between the two sides. Whether the gradient is measurable by our techniques will depend mainly on the size of the defect as well as on differential ventricular filling.

The formula derived for calculation of the cross-sectional area of atrial septal defect orifices was as follows:

$$ADA = \frac{ADF}{44.5\sqrt{LA_m - RA_m}}$$

where ADA = atrial septal defect area in cm.^{2}
ADF = atrial septal defect flow in c.c. per second
LA_m = left atrial mean pressure in mm. Hg
RA_m = right atrial mean pressure in mm. Hg
$44.5 = C\sqrt{2g} = 1.0\sqrt{1960}$.

Atrial Defect Flow (ADF).—There has been some question as to whether a unidirectional shunt occurs in atrial septal defect.[34,35,36] In the patients presented here, however, in whom the interatrial gradient was measurable, pressure in the left atrium exceeded that in the right during all phases of the cardiac cycle, and there was a normal oxygen saturation of arterial blood. Therefore, it is believed that shunt flow continued during the entire cardiac cycle. This has been measured in cubic centimeters per second. The calculation of atrial shunts has been described elsewhere.[30]

Atrial Defect Pressure Gradient ($P_1 - P_2$ or $LA_m - RA_m$).—P_1 is left atrial mean pressure (or pulmonary "capillary" mean pressure[16]), and P_2 is right atrial mean pressure.

Empirical Constant.—The value 1.0 is tentatively in use.

Methods.—Data were obtained by cardiac catheterization.* Pressures were measured in the left and right atria, respectively. The catheter was introduced into the pulmonary artery where a pulmonary cardiac output was measured. Following this, sampling was carried out in both superior and inferior venae cavae for estimation of peripheral blood flow. The shunt flow was determined as described elsewhere.[30] Although the patients were at rest throughout the study, it is possible that some error was introduced because pressures and blood flows could not be obtained simultaneously or even in quick succession. The greatest source of error lies in estimation of blood flow when the shunt is large. Here the arteriovenous oxygen differences may be so small that the error of the Van Slyke technique itself may affect the estimation by as much as 50 per cent.

*In the laboratory of Dr. James W. Dow, Children's Medical Center, Boston, Mass.

Results.—Data are presented on two patients in Table IX. In each patient a measurable interatrial gradient could be detected. The calculated areas of the orifice of the defects were 1.0 and 1.9 cm.^{2}, respectively.

Discussion.—Only two of eight patients with atrial septal defect studied in this and in the laboratory of Dr. Dow had measurable differences of pressure in the two atria. In these two patients where a difference of pressure was recorded, the area of the defect could be calculated. These patients had relatively small shunt flows. In the other six patients, the size of the defect could not be calculated because no measurable gradient was recorded. These patients had huge shunt flows indicating from the orifice formula that they had very large defects. The situation here is similar to that which occurs at the normal mitral valve where large volumes of blood flow in a brief period apparently without a recordable difference of pressure. The point at which pressures tend to equalize in the two atria so that the gradient becomes immeasurable is related to the size of the defect and the volume of the shunt.

This calculation has little surgical application because in those patients in whom the defect area can be calculated, the defect is so small that surgical repair is usually not indicated.

TABLE IX. DATA RELATIVE TO CALCULATION OF THE AREA OF ATRIAL SEPTAL DEFECT

PATIENT	FLOW PERIOD (SECONDS PER MINUTE)	SHUNT OUTPUT (LITERS PER MINUTE)	ATRIAL DEFECT FLOW (C.C. PER SECOND)	PRESSURES (MM. Hg)		ATRIAL DEFECT AREA (CM.^{2})
				LEFT ATRIAL MEAN	RIGHT ATRIAL MEAN	
1	60	5.5	92	7	3	1.0
2	60	7.1	118	7	5	1.9

VENTRICULAR SEPTAL DEFECT

Shunting through a ventricular septal defect is the result of a pressure difference between the two ventricles consequent on the size of the defect and the different volume-elasticity properties of the two ventricles. The cross-sectional area of the defect orifice may be calculated in two ways by the orifice formula.

The first formula for calculating the area of a ventricular septal defect is as follows:

$$VDA = \frac{VDF_m}{44.5\sqrt{LV_m - RV_m}}$$

where VDA = ventricular defect area in cm.^{2}
VDF_m = ventricular defect mean flow in c.c. per second
$44.5 = C\sqrt{2g} = 1.0\sqrt{1960}$
LV_m = left ventricular mean pressure in mm. Hg
RV_m = right ventricular mean pressure in mm. Hg.

Ventricular Defect Mean Flow (VDF_m).—Ventricular defect flow usually occurs throughout the cardiac cycle due to pressure differences during diastole

as well as during systole. The mean rate of shunt flow is measured in cubic centimeters per second. The calculation of shunt has been described elsewhere.[30]

Ventricular Defect Pressure Gradient ($P_1 - P_2$ or $LV_m - RV_m$).—P_1 is left ventricular mean pressure during the cardiac cycle, which may be obtained by left ventricular catheterization. Because left ventricular catheterization has not been undertaken in this laboratory, an alternative indirect method of approximating this pressure from our own data was used.

Although large discrepancies are said to occur between central and peripheral systolic mean pressures,[37] nevertheless the brachial arterial systolic mean pressure was used as an index of left ventricular systolic mean pressure. The period of ventricular systole per beat (sp) was measured directly on the right ventricular tracing, on the assumption that the difference in the duration of systole of the two ventricles in this disease is negligible. Pulmonary "capillary" mean pressure, which has been shown to be a good index of left atrial mean pressure,[16] has been used as an approximation of left ventricular mean diastolic pressure. This use of pulmonary "capillary" pressure is valid only in the absence of mitral stenosis. In occasional patients with severe tachycardia or elevated pulmonary blood flow, the rate of mitral valve flow may possibly be so increased as to require a measurable pressure gradient across the normal valve orifice. As a result, left atrial (and pulmonary "capillary") pressure may well exceed the left ventricular mean diastolic pressure by a few mm. Hg.[38] The period of ventricular diastole per beat (dp) was measured directly on the right ventricular tracing.

If the brachial artery systolic mean pressure is multiplied by the fraction $\frac{\text{systolic period, seconds per beat}}{\text{cardiac cycle, seconds per beat}}$, the pulmonary "capillary" mean pressure multiplied by the fraction $\frac{\text{diastolic period, seconds per beat}}{\text{cardiac cycle, seconds per beat}}$, and the two values summed, a number is obtained which gives a measure of the magnitude of the mean pressure in the left ventricle throughout the whole cardiac cycle. The errors so introduced by this indirect approach to the true mean pressure may be large in a given patient. No better indirect method is available, however. The error is minimized somewhat because the interventricular gradient is usually large, and the fact that the square root of the gradient is finally utilized in the formula further reduces the error. This is P_1 in the formula. The right ventricular mean pressure may be obtained directly either by electrical integration or by planimetric integration of the right ventricular pressure tracing during both systole and diastole. This is P_2 in the formula.

Empirical Constant.—This has not been worked out empirically because postmortem studies have not been available. For the present a value of 1.0 is being used for C.

The second formulas for calculating the area of a ventricular septal defect can be utilized for the calculation of phasic shunting and are as follows:

$$1.\quad VDA = \frac{VDF_s}{44.5\sqrt{LV_{sm} - RV_{sm}}}$$

$$2.\quad VDA = \frac{VDF_d}{44.5\sqrt{LV_{dm} - RV_{dm}}}$$

$$3.\quad (VDF_s \times SP) + (VDF_d \times DP) = F$$

where VDA = ventricular defect area in cm.²
VDF_s = ventricular defect mean systolic flow in c.c. per second
VDF_d = ventricular defect mean diastolic flow in c.c. per second
$44.5 = C\sqrt{2g} = 1.0\sqrt{1960}$
LV_{sm} = left ventricular mean systolic pressure in mm. Hg
RV_{sm} = right ventricular mean systolic pressure in mm. Hg
LV_{dm} = left ventricular mean diastolic pressure in mm. Hg
RV_{dm} = right ventricular mean diastolic pressure in mm. Hg
SP = systolic period in seconds per minute
DP = diastolic period in seconds per minute
F = shunt flow in c.c. per minute.

Ventricular Defect Flows, Systolic and Diastolic (VDF$_s$ and VDF$_d$).—These values are not known. They are related to one another, however. If equations (1) and (2) are solved, then

$$4.\quad VDF_s = VDF_d \frac{\sqrt{LV_{sm} - RV_{sm}}}{\sqrt{LV_{dm} - RV_{dm}}}$$

If this equation is now substituted in equation (3),

$$5.\quad VDF_d = \frac{F}{\left(\frac{\sqrt{LV_{sm} - RV_{sm}}}{\sqrt{LV_{dm} - RV_{dm}}} \times SP\right) + DP}$$

the values for phasic flow may be calculated if shunt flow, F, is known.

Ventricular Defect Pressure Gradient.—

A. Systolic pressure gradient ($P_1 - P_2$ or $LV_{sm} - RV_{sm}$): P_1 is the left ventricular systolic mean pressure. We have attempted to approximate this pressure by using brachial arterial systolic mean pressure as already described. P_2 is the right ventricular systolic mean pressure and may be obtained directly by integration with a planimeter of the right ventricular pressure tracing during systole.

B. Diastolic pressure gradient ($P_1 - P_2$ or $LV_{dm} - RV_{dm}$): P_1 is the left ventricular mean diastolic pressure. We have attempted to approximate this pressure by the use of pulmonary "capillary" mean pressure as previously described. P_2 is the right ventricular mean diastolic pressure which may be measured directly on the pressure tracing.

Methods.—Oxygen consumption was measured by the Benedict-Roth method just before the procedure. Samples for pulmonary blood flow were drawn with the catheter in the pulmonary artery, pressure in the pulmonary "capillaries" having been obtained previously, and in the right ventricle subsequently. Samples

TABLE X. DATA RELATIVE TO CALCULATION OF AREA OF VENTRICULAR SEPTAL DEFECT

PATIENT	SYSTOLIC PERIOD (SECONDS PER BEAT)	DIASTOLIC PERIOD (SECONDS PER BEAT)	PULSE RATE (PER MINUTE)	SYSTOLIC PERIOD (SECONDS PER MINUTE)	DIASTOLIC PERIOD (SECONDS PER MINUTE)	SHUNT FLOW (LITERS PER MINUTE)	PRESSURES (MM. Hg)						VENTRICULAR DEFECT FLOW MEAN (C.C. PER SECOND)	VENTRICULAR DEFECT FLOW SYSTOLIC (C.C. PER SECOND)	VENTRICULAR DEFECT FLOW DIASTOLIC (C.C. PER SECOND)	VENTRICULAR DEFECT AREA ($CM.^2$)
							BRACHIAL ARTERY SYSTOLIC MEAN (BA_{sm})	PULMONARY "CAPILLARY" MEAN ("Pc_m")	(BA_{sm} + "Pc_m") MEAN	RIGHT VENTRICLE SYSTOLIC MEAN	RIGHT ATRIAL MEAN	RIGHT VENTRICLE MEAN				
H. B.	0.37	0.36	82	30.5	29.5	5.0	136	16	74	100	14	59	83	133	31	0.5
K. H.	0.40	0.35	80	32	28	3.3	92	17	57	56	13	36	55	81	27	0.3
B. T.	0.39	0.32	85	33	27	3.6	100	10	60	28	7	19	60	95	19	0.2

for peripheral blood flow were drawn simultaneously with right ventricular pressures. The peripheral arterial pressure was measured shortly after the peripheral blood flow samples were drawn. The method of calculating shunt has been described elsewhere.[30] Systolic and diastolic periods (second per beat) were measured directly on the right ventricular tracing and the periods per minute obtained by multiplying each by the pulse rate per minute. It is appreciated that the interspersing of blood samples and pressures may introduce error into the calculation.

Observations.—In Table X are presented the pertinent measured and calculated data in three patients* with isolated ventricular septal defect. Cross-sectional areas of 0.5, 0.3, and 0.2 cm.^{2} were calculated from the data. This allowed shunts of 5, 3.3, and 3.6 liters per minute, respectively, to pass through the defect.

Discussion.—The first formula may be used for calculating the area from mean pressure and mean flow data. The use of this formula is valid only when the interventricular pressure gradient is unidirectional throughout the cardiac cycle, that is, when there is no arterial oxygen unsaturation. The second set of formulas are useful for two purposes. Equations (1) or (2) may be used to calculate the area of the defect when a pressure gradient exists only during one phase of the cardiac cycle. Equations (3) and (4) may be applied to determine the proportionate amounts of shunting during each phase of the cardiac cycle. When both the mean and phasic formulas are used for calculating the area of a ventricular septal defect, there will be minor differences in the answers derived due to the numerous electrical and planimetric measurements required for calculating the various pressure values entering the formulas.

The major errors in the formula, as we have used it, are in the methods employed. The method of indirectly estimating left ventricular pressures, the large variables in calculating the blood flow through the shunt,[30] and the time lag between recording of the different pressures and obtaining blood flows make the calculation, as it now stands, more an index than an absolute value of septal defect area. The use of left ventricular pressures in the equation would, of course, eliminate a large source of error here.

As in the case of atrial septal defect, the point at which ventricular pressures equalize and the gradient is no longer measurable is related to the size of the defect and the volume of shunt.

SUMMARY

1. Standard hydrokinetic orifice formulas have been applied to stenotic mitral, pulmonic, tricuspid, and aortic valves, patent ductus arteriosus, and atrial and ventricular septal defects. These formulas were considered applicable because of the high kinetic energy losses through small orifices or in the presence of high volume flow.

*Two of the patients were studied in the laboratory of Dr. James W. Dow, Children's Medical Center, Boston, Mass.

2. In its general form, the formula is as follows:

$$A = \frac{F}{C\sqrt{2gh}}$$

where A = cross-sectional area in cm.^{2} of the orifice
F = flow rate in c.c. per second
C = empirical constant
g = gravity acceleration
h = pressure gradient across the orifice in mm. Hg.

3. Cross-sectional valve areas have been calculated in twenty-one patients with mitral stenosis. Calculated and measured areas have checked within 0.2 cm.^{2} in six post-mortem examinations and in five patients at the time of operation. Repeated calculations from different sets of data in the same patient have checked well in all instances. Valve area showed a good correlation with severity of pulmonary symptoms. Changes in valve area following finger fracture valvuloplasty were observed in two patients. The exponential relation of pressure to flow and valve area is briefly discussed.

4. The stenotic cross-sectional area has been calculated in ten patients with pulmonic stenosis with one post-mortem observation and in two patients with patent ductus arteriosus with operative correlations.

5. Calculations have likewise been made but without post-mortem confirmation in tricuspid stenosis, atrial septal defect, and ventricular septal defect. Formulas are presented for calculation of the size of the aortic orifice in aortic stenosis. In these groups, the empirical constant, C, has not as yet been determined and must await the collection of post-mortem data.

6. In each case an attempt has been made to assess the sources of error as well as the degree of accuracy involved in the particular formula.

7. The chief value of these formulas is that they present an objective evaluation of surgical procedures designed to widen stenotic orifices or to abolish abnormal shunts. Furthermore, a theoretical prediction of the benefit to be derived from surgical widening of stenotic valves may be made.

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STUDIES OF THE CIRCULATORY DYNAMICS IN MITRAL STENOSIS. II.

Altered Dynamics at Rest

R. Gorlin, M.D.,* F. W. Haynes, Ph.D., W. T. Goodale, M.D.,**
C. G. Sawyer, M.D.,*** J. W. Dow, M.D., and L. Dexter, M.D.

Boston, Mass.

IT HAS been recognized for many years that mechanical narrowing of the mitral valve from fibrosis and calcification following rheumatic fever is responsible for the clinical symptoms of mitral stenosis.[1] Early studies demonstrated a low cardiac output,[2,3,4] wide arteriovenous oxygen differences,[5] and small stroke volume[2] in this condition.

Experimental studies of acute mitral stenosis[6,7] in animals have demonstrated an elevation of left atrial and pulmonary venous pressures (3 to 6 mm. Hg), although it was claimed that pulmonary arterial and right ventricular pressures failed to rise until pulmonary blood volume was artificially increased.

Beyond this general thesis, little knowledge was added concerning changes in pulmonary pressure dynamics and the physiologic sequence of events until the advent of cardiac catheterization, due to failure to produce chronic experimental mitral stenosis. Bloomfield and associates[8] first demonstrated an elevated right ventricular pressure in patients with mitral stenosis. Hickam and Cargill[9] first demonstrated inordinately elevated pulmonary arterial pressures, while Ellis and Harken[10] and Dexter[11] first reported elevations of pulmonary "capillary" pressure. It is the purpose of this series of papers to describe the deviations from the normal in circulatory pattern in patients with mitral stenosis and to relate physiologic responses and clinical symptoms to the severity of the mitral stenosis and to the magnitude of the pulmonary vascular changes seen in this disease.

CLINICAL MATERIAL AND METHODS

Twenty-one patients with stenosis of the mitral valve predominantly and minimal degrees of other valvular involvement were studied a total of twenty-three times. In Table I is seen a list of our patients arranged according to the calculated mitral valve orifice area[12] and classified as proposed by the New York Heart Association.[13] The degree of limitation ranged from Class I to Class IV.

From the Medical Clinic, Peter Bent Brigham Hospital, the Department of Pediatrics, Children's Medical Center, and the Departments of Medicine and Pediatrics, Harvard Medical School, Boston.

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*United States Public Health Service Research Fellow of the National Heart Institute.

**Life Insurance Medical Research Fellow.

***Research Fellow of the American Heart Association.

Patients were studied in a fasting state or else an hour or more following a light breakfast of black coffee, toast, and jam. Approximately one-fifth of the patients received Demerol Hydrochloride, 50 to 100 mg. intramuscularly, either before or during the study for relief of severe anxiety or respiratory symptoms. Cardiac catheterization was carried out in the usual fashion. Pulmonary "capillary" pressure was measured as described elsewhere.[14] The catheter was then withdrawn to the pulmonary artery in the region of the bifurcation. A No. 21 needle connected with a saline solution drip was introduced into either the brachial or radial artery. When pulse and respiratory rates were stable, cardiac output was determined by the direct Fick principle. Expired air was collected for three minutes in a Douglas bag. The volume was measured in a Tissot spirometer. Oxygen and carbon dioxide concentrations were measured by the Haldane-Henderson method. In most experiments, oxygen alone was measured by the Pauling oxygen analyzer. From previous studies with Haldane analysis of expired air, a mean correction factor of 1.007 was derived for converting expired volume to inspired volume under resting conditions.[15] The volume of oxygen inspired was calculated as per cent inspired oxygen, times volume of expired air, times 1.007. Midway during collection of the expired air, blood samples were withdrawn from the pulmonary and from the systemic arteries simultaneously and analyzed for oxygen content, capacity, and saturation by the method of Van Slyke and Neill,[16] and the arteriovenous oxygen difference was calculated. Pressures were recorded in the pulmonary artery and systemic artery simultaneously immediately after withdrawal of blood samples.

In four patients oxygen consumption was determined by the Benedict-Roth method, as described in a previous publication.[17]

Pressures were recorded with Hamilton manometers[18] or, in the latter part of the series, with electromanometers*[19] recording on a multi-channel, direct-writing oscillograph. A saline manometer was used for checking mean pressures but not for analytical purposes. Mean pressures were obtained by planimetric integration of the pressure tracings, when the Hamilton manometer was used, and by electrical integration of the oscillograph tracings. The zero point for all pressures was 10 cm. anterior to the back, with the patient in the recumbent or semireclining position.

Mitral valve orifice areas were calculated as described elsewhere[12] by the following formula:

$$MVA = \frac{MVF}{31\sqrt{\text{"PC"} - 5}}$$

where MVA = mitral valve area, cm.^{2}

MVF = mitral valve flow, c.c. per second $\left(\frac{\text{cardiac output, c.c. per minute}}{\text{diastolic filling period, seconds per minute}}\right)$

"PC" = pulmonary "capillary" pressure, mm. Hg

5 = assumed left ventricular mean diastolic pressure, mm. Hg

31 = empirical constant.

*Sanborn Company, Cambridge, Mass.

TABLE I. PHYSIOLOGIC DATA IN PATIENTS WITH MITRAL STENOSIS

PATIENT	CLINICAL CLASSIFICATION	MITRAL VALVE AREA (CM.²)	RHYTHM	ARTERIAL OXYGEN SATURATION (%)	OXYGEN CONSUMPTION (C.C. PER MINUTE)	A-V OXYGEN DIFFERENCE (C.C. PER LITER)	CARDIAC OUTPUT (LITERS PER MINUTE)	CARDIAC INDEX (LITERS PER MINUTE PER SQ. M.)	PULSE RATE (PER MINUTE)	STROKE INDEX (C.C PER BEAT PER SQ. M.)	A-P DIAMETER OF CHEST (CM.)	MEAN PRESSURES (MM. Hg)				RESISTANCES (DYNES SEC. CM.$^{-5}$)			WORK OF VENTRICLES AGAINST PRESSURE (Kg. M. PER MINUTE PER SQ. M.)	
												PULMONARY ARTERY	PULMONARY "CAPILLARY"	BRACHIAL ARTERY	RIGHT AURICLE	PULMONARY ARTERIOLAR	TOTAL PULMONARY	TOTAL SYSTEMIC	RIGHT VENTRICLE	LEFT VENTRICLE
J. D.	I	2.5	SR	100	281	30	9.4	5.2	100	52	18	25	19	91	9	51	212	775	1.2	6.4
J. F.	II	1.6	SR	99	254	39	6.5	3.8	72	54	22	32	21	92	9	135	394	1130	1.3	4.8
L. B.	II	1.4	SR	98	203	42	4.8	3.3	90	37	17	24	20	65	4	67	400	1082	0.95	2.8
L. C.	IV	1.4	SR	97	260	48	5.4	3.3	104	34	18	75	27		9	711	1110		3.1	
J. M.	II	1.3	SR	99	230*	53	4.4	2.7	108	25	18	33	25		0	145	600		1.3	
Gr.	III	1.1	SR	89	315	45	7.0	4.6	100	46	17	42	32	82	8	114	480	936	2.3	5.1
				89	239*	51	4.7	3.0	120	25	17	51	38		3	221	866		2.1	
Ba.	IV	0.9	SR	97	291	56	5.2	3.6	105	35	18.5	69	32	81	−3	569	1062	1245	3.7	3.9
L. T.	III	0.9	SR	99	262	59	4.4	2.5	70	35	18	45	24	71	5	382	820	1290	1.4	2.4
R. C.	IV	0.9	SR	93	315	60	5.3	3.5	108	33	20	75	39	93	5	544	1130	1405	3.5	4.4
M. B.	IV	0.8	AF	94†	194	61	3.2	2.0	96	20	18	23	17		14	150	574		0.26	
M. T.	IV	0.7	SR	97	196	62	3.2	2.4	79	31	20	30	21		5	225	750		0.86	
E. S.	IV	0.7	AF	97	216	55	3.9	2.4	80	31	19	48	26	96	4	451	984	1970	1.5	3.1
				97	190	58	3.3	2.1	84	24	19	38	28		6	242	921		0.96	
W. F.	IV	0.6	AF	99	189	72	2.6	1.8	80	22	18.5	60	23	90	8	1139	1845	2770	1.3	2.2
E. D.	III	0.6	AF	97	212	60	3.5	2.4	140	17	20	54	36	98	12	411	1235	2240	1.5	3.2
N. L.	IV	0.6	SR	85	272	86	3.2	1.9	105	18	19	66	28	83	14	950	1650	2080	1.4	2.1
M. G.	IV	0.6	SR	90	176*	65	2.7	2.0	82	24	19	80	30		15	1480	2372		1.9	
McL.	III	0.6	AF	81	330	78	4.2	2.4	105	23	18	94	54	123	33	762	1790	2340	2.1	4.1
R. W.	IV	0.6	SR	99	163	46	3.5	2.6	70	38	18	46	34	69	9	274	1050	1580	1.4	2.4
D. K.	IV	0.5	SR	80	173*	70	2.5	1.8	204	9	18	54	46	69	4	256	1730	2210	1.3	1.7
M. M.	IV	0.4	AF	99	154	66	2.3	1.4	56	25		55	22	108	10	1150	1915	3760	0.90	2.1
D. V.	IV	0.4	SR	92	163	54	3.0	2.6	100	26	13	63	35	75	7	746	1680	2000	2.1	2.6
Average				94	235	57	4.3	2.8	98	30		51	29	87	8	491	1111	1799	1.7	3.3

SR = sinus rhythm
AF = auricular fibrillation
*Benedict-Roth method.
†Blood sample drawn immediately after procedure.

The resistances were calculated according to the Poiseuille equation, where $\text{Resistance} = \frac{\text{Pressure gradient}}{\text{Rate of blood flow}}$. Pulmonary arteriolar resistance was calculated as follows:

$$R = \frac{PA_m - \text{“}PC_m\text{”}}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

Total pulmonary resistance was calculated as follows:

$$R' = \frac{PA_m - O}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

Total peripheral resistance was calculated as follows:

$$R'' = \frac{BA_m - O}{CO} \times 1{,}332 \text{ dynes seconds cm.}^{-5}$$

where PA_m = pulmonary arterial mean pressure, mm. Hg
“PC_m” = pulmonary “capillary” mean pressure, mm. Hg
BA_m = brachial arterial mean pressure, mm. Hg
CO = cardiac output, c.c. per second
1,332 = conversion factor from mm. Hg to dynes per cm.^{2}

These calculations are based on the belief that the total resistance against which a ventricle works must include the work done in distending the other ventricle in diastole, that is, for the pulmonary circuit this includes the resistance offered by the pulmonary vasculature, the mitral valve, and the left ventricle in diastole. For the systemic circuit, it includes the resistance offered by the systemic vasculature and the right ventricle in diastole.

Ordinarily, ventricular work against pressure has been calculated using the pulmonary or brachial arterial mean pressure as an approximation of ventricular mean systolic ejection pressure.[20,21] This type of calculation does not take into account the fact that the ventricle actually elevates pressure only from its diastolic filling pressure to systolic ejection pressure. The error introduced in estimation of ventricular work load is small in the presence of a normal filling pressure, but it is considerable in the presence of an elevated filling pressure.

Pulmonary pressure work and systemic pressure work are each composed of two components—that contributed by the discharging ventricle itself and that contributed by the other ventricle in elevating its filling pressure. Here we shall be concerned with that fraction of work contributed to each circuit by the discharging proximal ventricle. For the pulmonary circuit, in the absence of tricuspid and pulmonic stenosis, the right ventricular pressure fraction is measured from right atrial mean pressure to pulmonary arterial mean pressure. For the

peripheral circuit, in the absence of aortic stenosis, the left ventricular fraction is measured from assumed left ventricular diastolic pressure[12] to brachial arterial mean pressure.

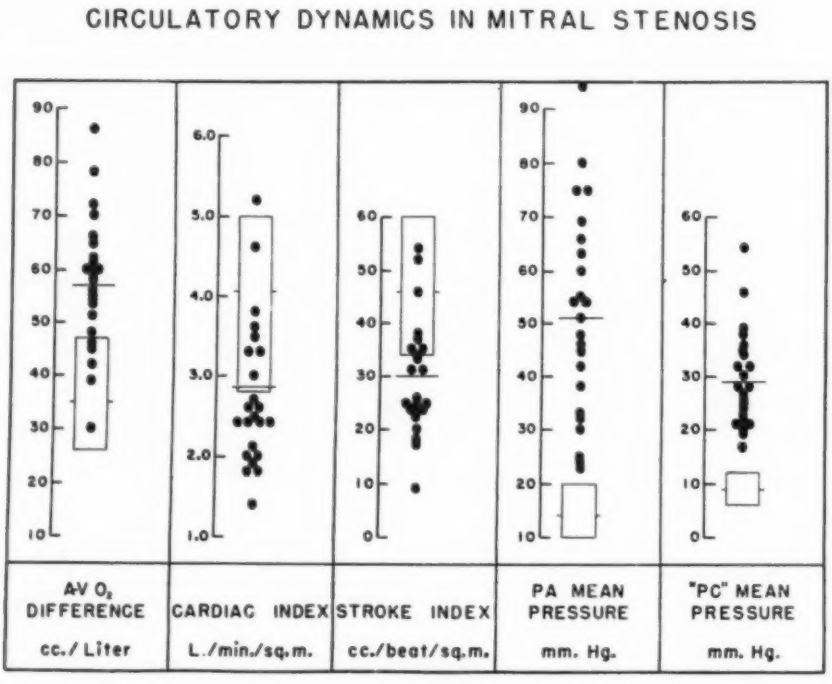

Fig. 1.—The values for each patient with mitral stenosis at rest are plotted as black circles with the long horizontal line the average value for the group. The rectangles serve as a reference zone representing the variation seen in eight normal individuals studied in this laboratory with the short horizontal lines the mean for the group. *PA* = pulmonary artery; "*PC*" = pulmonary "capillary."

The formulas used for ventricular work are as follows:

$$W_R = \frac{(CI \times 1.055)\ ([PA_m - RA_m] \times 13.6)}{1000} \text{ kg.M. per minute per sq.M.}$$

$$W_L = \frac{(CI \times 1.055)\ ([BA_m - 5] \times 13.6)}{1000} \text{ kg.M. per minute per sq.M.}$$

where W_R = work of right ventricle against pressure
W_L = work of left ventricle against pressure
CI = cardiac index, liters per minute per sq.M.
1.055 = specific gravity of blood
PA_m = pulmonary arterial mean pressure, mm. Hg
RA_m = right atrial mean pressure, mm. Hg
BA_m = brachial arterial mean pressure, mm. Hg
5 = assumed left ventricular diastolic pressure, mm. Hg
13.6 = specific gravity of mercury.

OBSERVATIONS

Pertinent data are contained in Table I and are plotted in Figs. 1 and 2 against the range of normal values seen in this laboratory. Oxygen consumption per square meter of body surface area at rest usually showed values within the normal range or somewhat higher, presumably due to the discomfort of dyspnea. In no instance were values for oxygen consumption below the normal range.

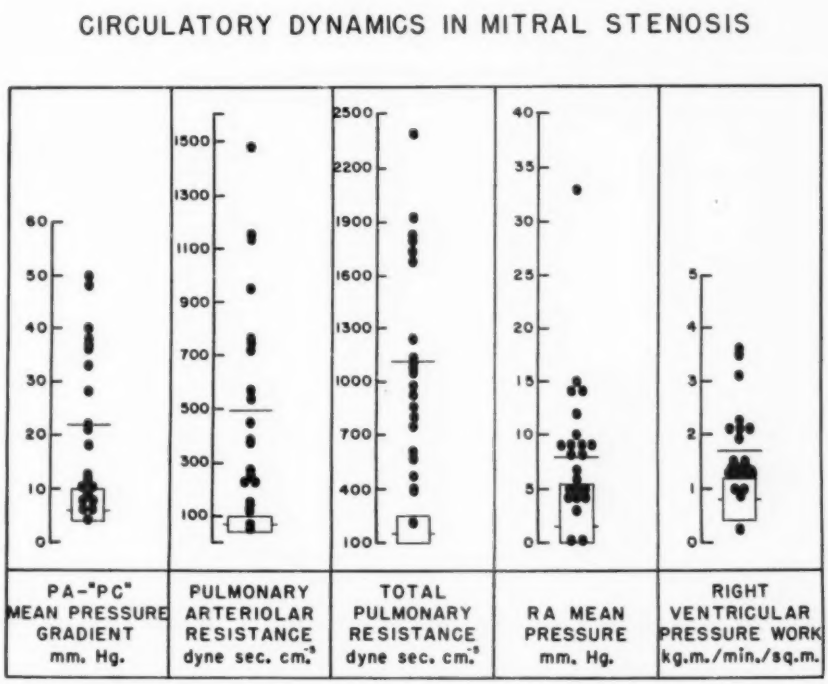

Fig. 2.—The values for each patient with mitral stenosis at rest are plotted as black circles with the long horizontal line the average value for the group. The rectangles serve as a reference zone representing the variation seen in eight normal individuals studied in this laboratory with the short horizontal lines the mean for the group. *PA* = pulmonary artery; "*PC*" = pulmonary "capillary"; *RA* = right atrium.

Tissue oxygen extraction, as measured by the arteriovenous oxygen difference, was considerably elevated above normal in the majority of these patients (Fig. 1). Although cardiac output per square meter of body surface area was below the normal average for the group as a whole, a wide range of values was observed. In fact, normal cardiac outputs were seen in seven patients. Cardiac output, however, bore no consistent relationship to the severity of the mitral stenosis. In approximately one-half of the patients, pulses of 100 or over were observed at rest. In association with the generally low cardiac output and the increased pulse rate, stroke output per square meter of body surface area on the average was low.

Six patients had auricular fibrillation. Cardiac index in this group tended to be lower than that of patients with normal sinus rhythm at similar pulse rates.

Pulmonary arterial pressures were elevated two to six times the normal values, although in three individuals (J. D., L. B., and M. B.) the pressures were only slightly above normal (Fig. 1). Pulmonary "capillary" pressures showed a wide range of values with the average considerably above the normal of 6 to 12 mm. Hg. It is of interest that one patient (M. B.) with proved mitral stenosis had an almost normal pulmonary "capillary" pressure during the time of study.

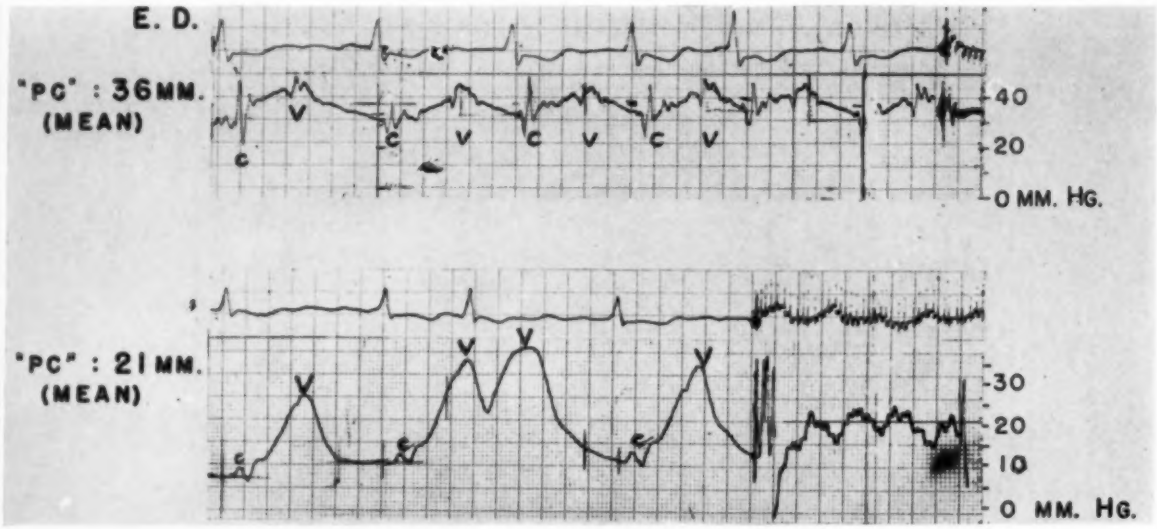

Fig. 3.—Pulmonary "capillary" pressures with simultaneous electrocardiograms (Lead II). In the upper figure is seen a pulmonary "capillary" pressure pulse in a patient with severe mitral stenosis without regurgitation. In the lower figure is seen the pressure pulse in a patient with both mitral stenosis and regurgitation. At the right, mean pressures are recorded. There are no A waves because of auricular fibrillation. C waves occur at the time of closure of the mitral valve. V waves are synchronous with ventricular systole. Note the comparatively small and normal size of the V waves in the upper tracing and the large V waves in the presence of mitral regurgitation (lower tracing).

In Fig. 3, the upper tracing shows the pulmonary "capillary" pressure contours of patient E. D. The generally flat pattern of the curve and small V wave indicated little or no mitral regurgitation. This pattern was seen in most of the patients of this series. In the lower tracing of Fig. 3 is seen the high spiking V wave characteristic of mitral insufficiency.[22] The pulmonary artery-pulmonary "capillary" mean pressure gradient (Fig. 2) ranged from normal to greatly increased values, the average being considerably higher than the average normal of 5 to 10 mm. Hg. In the majority of the patients, pulmonary arteriolar resistances were considerably elevated above the normal value of 70 dynes seconds cm.$^{-5}$ In the two mildest cases (J. D. and J. F.), the arteriolar resistance was within the normal range. As reported previously,[21] when pulmonary "capillary" pressures approached 25 mm. Hg (the approximate colloid osmotic pressure of plasma), the pulmonary artery-pulmonary "capillary" pressure gradient and the pulmonary arteriolar resistance tended to rise, as seen in Fig. 4, although not always in proportion to the particular elevation in pulmonary "capillary" pressure obtained during a single resting study.

In many patients, severe valvular stenosis was associated with an elevation of pulmonary arteriolar resistance. There were striking exceptions to this, however. For example, patient L. C., whose valvular orifice area was 1.4 cm.^{2}, had a resistance of 711 dynes seconds cm.$^{-5}$ Conversely, patients D. K. and R. W. had comparatively low resistances, although their valvular areas were 0.5 and 0.6 cm.^{2}, respectively.

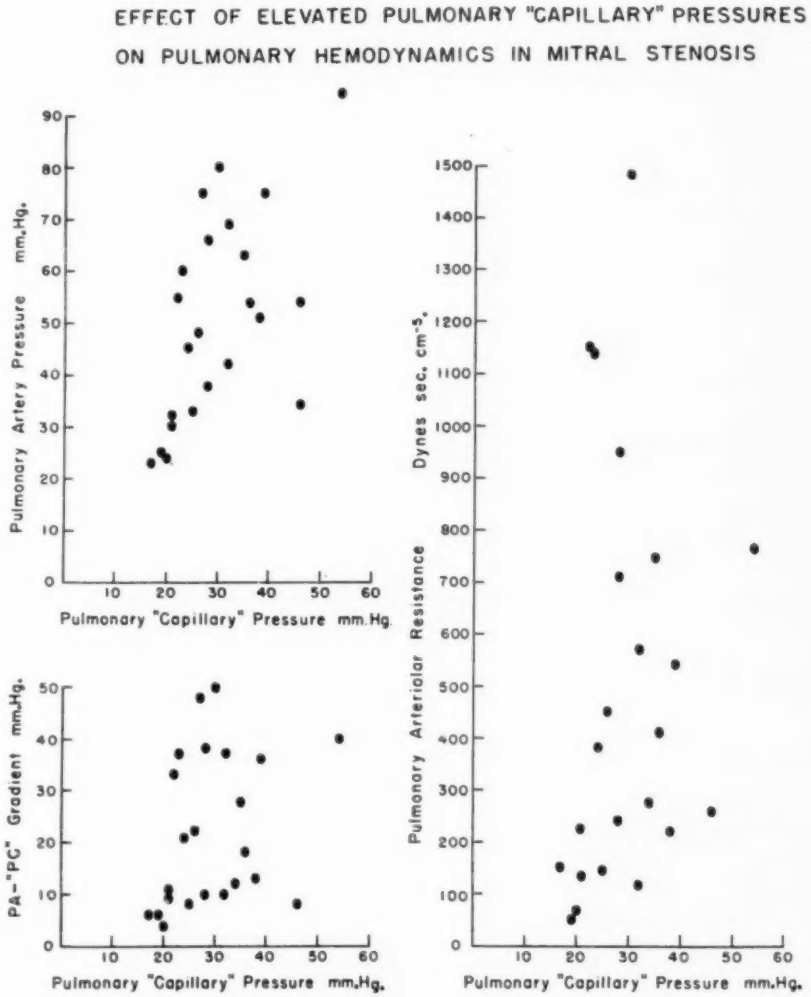

Fig. 4.—Relationship of pulmonary "capillary" pressure to pressure in the pulmonary artery, the pressure gradient, and pulmonary arteriolar resistance in mitral stenosis. Note the striking increase in these factors as the pulmonary "capillary" pressure approaches 25 mm. Hg. See text for significance of these findings.

When the total resistance of the pulmonary circuit was plotted against stroke output per square meter, an inverse relationship was found, as seen in Fig. 5. In the nine patients where total pulmonary resistance was above 1,200 dynes seconds cm.$^{-5}$ there was a stroke index of 26 c.c. per beat per square meter or less.

Right atrial mean pressures (Fig. 2) averaged 5 mm. Hg higher than in normal patients, with values ranging up to 33 mm. Hg. Because no patient had physiologic evidence of tricuspid stenosis by pressure measurements in the right ventricle during diastole and in the right atrium, right atrial mean pressures were considered as indicative of the true filling pressure of the right ventricle during diastole.[15] As judged by these filling pressures, 50 per cent of the patients showed evidence of right ventricular incompetency even at rest. Work of the right ventricle against pressure (Fig. 2) was increased about twofold, due in most cases to the large elevation of pressure required. Some patients had normal filling pressures despite greatly increased pressure work.

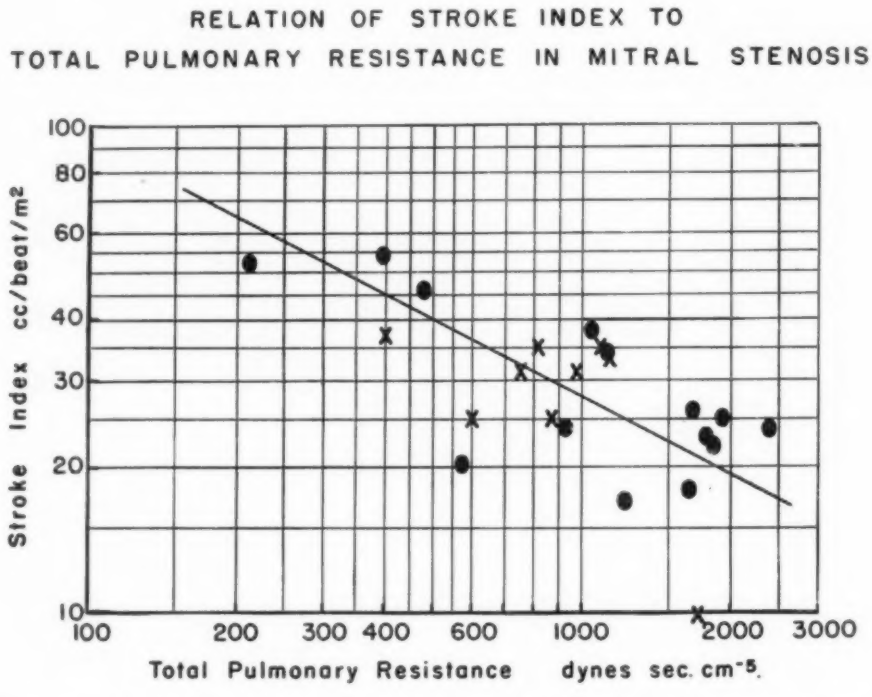

Fig. 5.—Stroke index in mitral stenosis is plotted against total pulmonary resistance. The crosses are those patients with normal right atrial mean pressures. The solid dots are those whose right atrial mean pressures exceeded 5 mm. Hg. Note the straight-line logarithmic relationship between stroke index and resistance ($r = -0.638$).

Brachial arterial pressures approximated the normal average. Calculated peripheral resistance was higher than normal in association with the low cardiac outputs. Left ventricular work against pressure was calculated to be slightly less than normal, due in the main to a lower volume of blood being discharged.

Six patients (Gr. in both studies, R. C., E. D., McL., D. K., and D. V.) were in different stages of clinical pulmonary edema at rest. Symptoms of pulmonary edema usually occurred whenever pulmonary "capillary" pressure approached or exceeded 35 mm. Hg. Arterial oxygen saturation was below normal in five of these six patients. A decreased saturation was seen in two others

who probably had severe degrees of pulmonary vascular disease, as judged by the calculated pulmonary arteriolar resistances. For the rest of the group, arterial oxygen saturation was normal.

DISCUSSION

The mitral valve is located at one of the most vulnerable points in the circulatory system because it is the sole exit from the pulmonary bed into the left ventricle and peripheral circulation. The peripheral cardiac output is dependent on the amount of blood discharged by the left ventricle, and this in turn will depend on the amount of blood which flows into the ventricle through the mitral valve. Rate of flow through this valve depends upon the pressure gradient across the valve.[12] It follows that any narrowing or stenosis of the mitral valve will necessitate an increase in left atrial and pulmonary vascular pressures in order to maintain an adequate left ventricular inflow. In the patient with mitral stenosis, there will develop a certain equilibrium between pressure and flow. If this equilibrium is upset, there will occur either a rise in pressure in the pulmonary circuit or a fall in cardiac output.

Although wide ranges of values for pressures and flows were observed in mitral stenosis, the over-all pattern was for pressures in the pulmonary circuit to rise somewhat[8-11,23] and for the peripheral cardiac output to decrease somewhat.[2,3,4,10,11,23] A normal oxygen consumption was maintained by a reciprocal adjustment between the cardiac output and the arteriovenous oxygen difference, namely tissue oxygen extraction per cubic centimeter of blood. The decrease in cardiac output was associated with a fall in stroke index. Both extremes in the pressure-flow equilibrium were seen in this group of patients. For example, in patient Gr., peripheral oxygen consumption and cardiac output were of such a magnitude as to be associated with an elevation of the pulmonary "capillary" pressure above the colloid osmotic pressure of plasma, which resulted in pulmonary edema during the studies. The opposite situation was seen in another patient, M. B., whose peripheral oxygen and blood flow demands were so low that pulmonary "capillary" pressure was almost within the normal range at the time of study, despite severe valvular stenosis. It is obvious that there were large differences in the basality of the patients in this group to account for some of the differences in the circulatory responses. Reports in the literature[9,10,23] have indicated both normal and low cardiac outputs in patients with mitral stenosis. In our own series, normal and high outputs were seen either in patients with a mild form of mitral stenosis, as in patients J. D., J. F., and L. B. in whom the flows could be tolerated without pulmonary edema, or in patients who were not basal at rest, such as Gr. and R. C., whose ample cardiac outputs necessitated elevation of pulmonary "capillary" pressure above the transudation level.[24]

The patients with auricular fibrillation tended to have lower cardiac indices than those with normal sinus rhythm. Patients who had similar valve areas and pulse rates in the two groups were selected for comparison. This is in accord with the observations of others,[25,26,27] who believed that atrial systole contributed a significant portion of the left ventricular inflow. Pulmonary edema was not

a prominent feature in the clinical course of these fibrillators, provided tachycardia was controlled by digitalis. Our patients with normal sinus rhythm frequently had sudden episodes of tachycardia which resulted in pulmonary edema. As is well known, digitalis is not particularly effective in controlling the heart rate when the rhythm is sinus in origin. Since blood flows through the mitral valve only during diastole and diastole becomes shortened by tachycardia, blood flow can be maintained only by an elevation of the pressure proximal to the valve, which, in turn, entails elevation of the pulmonary "capillary" pressure to the point of producing pulmonary edema in some patients. The mechanism of production of pulmonary edema by tachycardia has been discussed in detail elsewhere.[24]

Six patients (Gr. in both studies, R. C., E. D., McL., D. K., and D. V.) were observed to be in pulmonary edema at rest, as indicated by the development of râles during the period of study. Each had pulmonary "capillary" pressures in excess of 30 mm. Hg. The shortcomings of making a precise hydrostatic analysis of edema formation by the technique employed have been discussed elsewhere.[21] Besides individual variation in plasma osmotic pressure, there is the major problem of where to place the zero point properly for pressure measurement. The ideal zero point should be taken with regard for the mean intrathoracic pressure and with respect only to the areas where pulmonary transudation is actually occurring. These factors cannot be determined easily in the human being. Instead, all of our pressures have been referred to a common zero point. The pressure, when this zero point is used, records only the hydrostatic pressure of the mid-chest. With the patient in the recumbent position, pressures in the posterior portions of the lung will be higher and those in the anterior portions lower than the value recorded at the arbitrary zero level. Although local pulmonary hydrostatic pressure cannot be accurately measured from a common zero point, its use is justified by the fact that we are concerned mainly with causes for the pressure elevation rather than the individual levels of pressure at which pulmonary edema occurs. Pulmonary edema in these patients, as will be discussed in a later report,[24] was always associated with either an increased cardiac output, an increased pulse rate, or an increased duration of left ventricular systole. The pressure-flow relationship was altered by increases in these factors such that the pulmonary pressures rose beyond the particular transudation level of each patient. That diffusion of oxygen was interfered with in these patients is attested to by the fact that five of six of these patients had abnormally low arterial oxygen saturations, ranging from 80 to 92 per cent.

In response to the alterations in pulmonary pressures, certain bodily changes take place. The rise in pulmonary arteriolar resistance in most patients was seen to parallel roughly the degree of mitral stenosis, although many exceptions were observed. As has been mentioned elsewhere,[21] however, whenever the pulmonary "capillary" pressure rose to levels around 25 mm. Hg or more, the pulmonary arterial mean pressure, pulmonary artery-pulmonary "capillary" mean pressure gradient, and the pulmonary arteriolar resistance tended to rise sharply. That this figure of 25 mm. Hg approaches the average plasma colloid osmotic pressure is significant, suggesting perhaps a cause and effect relationship

between abnormal capillary filtration and the precapillary resistance. The changes in arteriolar resistance presumably take place over a long period of exposure to elevated pulmonary "capillary" pressures. The failure of a more direct correlation of level of resistance in relation to pulmonary "capillary" pressure in some patients was probably due to two factors. First, we made only a single observation in each patient of the level of pulmonary "capillary" pressure in relation to resistance. It is entirely possible that the altered basality of some of the patients during the study may have occasioned an abnormally high pulmonary "capillary" pressure as compared to their average daily level of pressure. Second, whatever the nature of the pulmonary arteriolar response, there is probably a large individual variation of reactivity to the same stimulus.

In two patients with extreme elevation of pulmonary arteriolar resistance (N. L. and M. G.) in whom there was no evidence clinically of pulmonary edema, arterial oxygen saturations were 85 and 90 per cent, respectively. Presumably, the arterial oxygen unsaturation was attributable to pulmonary parenchymal disease alone, preventing normal oxygen diffusion between alveoli and capillaries in these individuals. No special studies to prove this point were made. That increased pulmonary arteriolar resistance and impaired oxygen diffusion do not necessarily coexist is indicated by patients M. M. and L. C. who had elevated resistances and normal arterial oxygen saturations. This random relationship between pulmonary arteriolar resistance and arterial oxygen saturation has likewise been seen in patients with pulmonary disease.[28] Pulmonary vascular disease per se does not necessarily interfere with the oxygenation of blood in the lung, and pulmonary parenchymal disease does not necessarily produce changes in the vasculature of the lungs in a wide variety of pulmonary diseases.[28] Whether parenchymal and vascular lesions go hand in hand or whether one is consequent to the other in mitral stenosis is as yet speculative. Because of the adaptability of the lung and its circulation, arterial oxygen saturation is not a sensitive index of the presence of parenchymal change, and, hence, full oxygen saturation does not preclude parenchymal disease. Whatever the cause, in the presence of severe mitral stenosis and high pulmonary vascular pressures, true pulmonary vascular disease does develop.[29,30]

As suggested by Meakins and associates twenty-seven years ago,[2] when the resistance to blood flow increases, the right ventricular output decreases. This has been our experience and, as shown in Fig. 5, there was a straight-line relation between cardiac and stroke indices on the one hand and total pulmonary resistance on the other, when plotted logarithmically ($r = -0.638$). There were occasional deviations from this relationship, suggesting that right ventricular myocardial function was a variable in the theoretical reciprocal relationship of flow to resistance. Those occasional patients (M. B. and M. T.) in whom cardiac output was below normal, despite a fairly low pulmonary circuit resistance, probably had definite myocardial insufficiency.

The effect of the increased resistance is expressed not only as a decrease in cardiac output, but frequently as an increase in the calculated right ventricular work against pressure. Work against pressure alone increases from two to four times the normal in mitral stenosis. The degree of work accomplished will

depend on the myocardial competency of the ventricle in question. If it is competent, normal quantities of blood elevated to almost systemic pressure levels may be discharged at a normal filling pressure (patient Ba.). As the ventricle fails, the work may still be performed, but at a greater diastolic fiber length, as evidenced by an elevated filling pressure, as in Gr. Ventricular competency depends on many factors. In the case of rheumatic heart disease, it will be dependent first upon the increased work load imposed by the valvular disease, which involves mainly the volume of blood and the resistance against which the ventricle must discharge, and, second, upon the state of the myocardium itself. In this group of patients over one-half had an elevated right ventricular filling pressure at the time of study. This evidence of incompetency was not correlated necessarily with the right ventricular pressure work load at the time, although it is true that those with the highest total resistances (M. G., M. M. and McL.) and those with the highest blood flows (J. D. and Gr.) all had an elevation of filling pressure. On the other hand, in patient M. B. the right ventricle performed only 0.26 kg. M. of useful work, although at a filling pressure of 14 mm. Hg. The right ventricle, then, was extraordinarily incompetent in the face of a low work load. This incompetency was presumably due to underlying rheumatic myocardial disease. Thus, depending on the intrinsic myocardial state in some patients, the right ventricle may fail sooner than in others at given levels of pulmonary circuit resistance or work load.

Those individuals who have essentially pure mitral stenosis usually have had a mild form of rheumatic fever.[31] The myocardium of these patients is usually not grossly abnormal histologically. These patients frequently develop paroxysmal pulmonary edema, as Bland and Sweet[32] pointed out, from an overactive right ventricle. The result of this overactivity is probably a momentary increase in right ventricular output over the left, such that pulmonary blood volume rises. Pulmonary "capillary" pressure rises according to the particular volume-pressure characteristics of the pulmonary venous bed,[24] with the eventual production in some patients of pulmonary edema. This was seen clearly in patients R. C. and Gr., who had only a moderately tight stenosis but maintained a normal output and a normal right ventricular filling pressure, despite a high total pulmonary circuit resistance. The right ventricle seems to be an important factor in producing paroxysmal pulmonary edema, in that sudden surges of output can occur if this ventricle is competent.

Because ventricles may fail at different work loads, it is always important to assay the right ventricular filling pressure with regard to the useful work output. If the bodily demands are low enough, for example, the cardiac output required may be so low that the right ventricle can meet the demand at a normal filling pressure. But stress, such as the procedure of cardiac catheterization, may so increase the demands for blood flow that the right ventricle must ascend the limb of a Starling curve in order to discharge more blood at a greater diastolic fiber length. Hence, one must be cautious in evaluating ventricular competency on the basis of a diastolic filling pressure only. Landis and co-workers[33] alluded to this when they reported that in dogs with certain circulatory defects right atrial pressures became elevated only on exercise. While the energy

release of a ventricle may be high and the efficiency low as regards useful work, these factors cannot be easily assessed in man. But it does seem clear that no matter what the efficiency, the degree of dilatation, as judged by filling pressure in relation to work done, gives a good index of the competence of the ventricle.

In response to the generally decreased peripheral cardiac output, certain peripheral adjustments take place. Among them, as already mentioned, is a greater tissue oxygen extraction, expressed as a greater arteriovenous oxygen difference, and an increase in the total peripheral resistance, probably reflecting a decrease in the total cross-sectional vascular bed.

SUMMARY

1. Twenty-one patients with mitral stenosis have been studied by the technique of cardiac catheterization. These patients were classified clinically and also according to the size of the orifice of the mitral valve. Six patients were in pulmonary edema during the study.

2. As a consequence of mitral valvular stenosis, a balance develops between pulmonary vascular pressures and peripheral blood flow (tending toward an increase in pulmonary pressure and a decrease in blood flow).

3. Cardiac and stroke indices were decreased at rest, although a wide range of values was seen. Patients with auricular fibrillation had slightly lower cardiac indices than patients with normal sinus rhythm. Tissue oxygen extraction per cubic centimeter of blood was increased so that oxygen consumption was maintained within the normal range in all.

4. Pulmonary "capillary" pressures were increased above normal as a result of the increase in left atrial pressure proximal to the mitral stenosis.

5. Pulmonary arterial pressures were increased above normal as a result of (a) the increase in pulmonary "capillary" pressure and (b) increased pulmonary arteriolar resistance.

6. The presence of an elevated pulmonary arteriolar resistance was roughly related to the level of pulmonary "capillary" pressure and the degree of valvular stenosis.

7. An inverse logarithmic relationship was observed between total pulmonary resistance and stroke output per square meter.

8. As a result of the increased pulmonary vascular pressures, the pressure work of the right ventricle was greatly increased.

9. Right ventricular incompetency, as judged by an elevated filling pressure, was seen in over one-half of the patients studied. Incompetence was believed due to (a) the increased pulmonary pressure load and (b) underlying myocardial damage from rheumatic fever.

The authors are indebted to Dr. James L. Whittenberger of the Harvard School of Public Health for the generous use of the facilities of his laboratory.

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CRITICAL RATES IN VENTRICULAR CONDUCTION

II. Simulation of Localized Bundle Branch Block

Harry Vesell, M.D.

New York, N. Y.

ATTENTION has been previously called[1] to a condition of unstable ventricular conduction which was noted in some patients with myocardial disease and which was closely related to a critical cardiac rate. At this critical rate there apparently existed in a bundle branch a delicate state of equilibrium between normal conduction and nonconduction or block, when a slight variation in rate, often as little as an increase or decrease of one beat per minute, changed conduction to block or block to conduction. This condition has been observed many times and is not so rare if carefully looked for and if the cardiac rate happens to vary while the electrocardiogram is being recorded.

An unusual manifestation of this phenomenon of altered conduction when the critical rate is exceeded is seen in the following.

M. I., an Italian laborer, 47 years of age, appeared at a medical clinic for examination, April 10, 1948. An electrocardiogram was taken and is shown in Fig. 1,*A*. It revealed a regular sinus rhythm with a rate of about 75 per minute. The P waves were normal. The P-R interval was 0.16 second. QRS was aberrant, measuring 0.13 second in duration in the standard limb leads where it was monophasic, upright, and notched. RS-T was depressed, and T was inverted in Leads I and II. In the precordial leads CF_1 and CF_4, the only precordial leads taken, the QRS was no longer aberrant. Its limbs were smooth, and the whole QRS complex measured only 0.08 second in duration. T was biphasic. Evidence of bundle branch block, probably left-sided, was present in the standard limb leads, while apparently normal ventricular conduction was recorded in the precordial leads. Such unusual localization of the electrocardiographic changes to certain leads might suggest an unusual anatomic localization of the block to certain parts of the left bundle branch. However, analysis of the cardiac rates showed the range to be from 80 to 68 beats per minute (R-R interval 0.75 to 0.88 second) during the taking of the standard leads and slower, 68 to 60 per minute (R-R interval 0.88 to 1.00 second), for the precordial leads. This localization of the block to the limb leads of the electrocardiogram was a fortuitous occurrence because the critical rate for ventricular conduction, 68 per minute, happened to be exceeded only while these leads were being recorded. During the taking of the precordial leads the rate became slower, 68 to 60, less than the critical rate, and so ventricular conduction was normal.

From the Cardiographic Laboratory, Beth Israel Hospital, New York.
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Another electrocardiogram was taken four days later and is shown in Fig. 1,*B*. In this record all the QRS complexes in all leads, the precordial as well as the limb leads, were aberrant. The duration of QRS was 0.13 second. The bundle branch block pattern was persistent throughout this entire tracing. The cardiac rates ranged from 71.4 to 85.7 per minute (R-R intervals 0.84 to 0.70 second). The cardiac rate was faster than the critical rate during the recording of the entire second electrocardiogram, and so impaired or blocked conduction down the left bundle branch, due to functional fatigue, occurred with each beat.

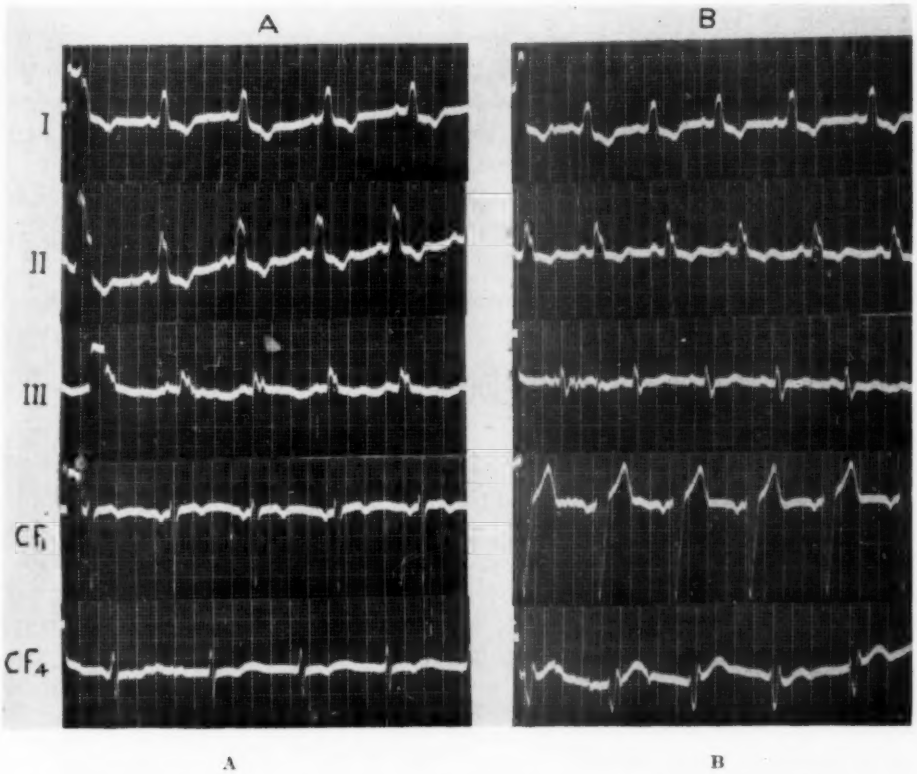

Fig. 1.—*A*, Electrocardiogram taken April 10, 1948. In Leads I, II, and III the QRS is aberrant, 0.13 second in duration: indicative of bundle branch block. In the precordial leads, CF_1 and CF_4, QRS is 0.08 second: evidence of normal intraventricular conduction. The cardiac rate is 68 to 80 for limb leads and 60 to 68 for precordial leads. *B*, Electrocardiogram taken four days after *A*. All QRS complexes in all leads, precordial as well as limb leads, are aberrant. The cardiac rate is 71.4 to 85.7.

It is possible, too, that bundle branch block may have become permanent by the time of the taking of the second electrocardiogram. The ventricular complexes representing bundle branch block were similar in the two electrocardiograms. Though it is possible to have a fortuitous localization of the electrocardiographic changes of bundle branch block to just one lead, this condition apparently is not the same as focal bundle branch block, described by Katz,[2] in which the QRS was found aberrant in Lead CF_2 only, but where the cardiac rate was not found to be related.

The pathologic anatomy of unstable bundle branch block has been previously discussed.[1] It may be added that the pathologic changes of peri-infarction, recently described,[3] also may be responsible.

SUMMARY AND CONCLUSION

In myocardial disease ventricular conduction may vary with cardiac rate. When a critical rate is exceeded, conduction in a bundle can be blocked and bundle branch block produced. If, as often happens, cardiac rate varies while the electrocardiogram is being taken, the critical rate can be exceeded at any time during the recording. During the taking of the electrocardiogram in Fig. 1,*A*, the cardiac rate was faster than the critical rate only while the standard leads were being recorded; it was slower while the precordial leads were taken, and so produced evidence of bundle branch block localized to the limb leads with normal ventricular conduction recorded in the precordial leads. This change in rate was fortuitous and if the order of slowing were the reverse (i.e., slower for the standard leads, faster in precordial leads), it most likely would have resulted in evidence of bundle branch block localized to the precordial leads. Functional changes of fatigue or recovery from fatigue were considered responsible for the fluctuations between conduction and block.

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DEPRESSION OF CARDIAC PACEMAKERS BY PREMATURE IMPULSES

A. Pick, M.D.,* R. Langendorf, M.D., and L. N. Katz, M.D.

Chicago, Ill.

RHYTHMICITY is one of the basic properties of the cardiac muscle. The actual and various potential pacemakers of the heart are located in the specific muscular system, and the order of their spontaneous impulse formation is governed by the law of the heart.[1] Whereas the rate of the impulses formed in centers of higher activity like the S-A and A-V nodes is variable and is regulated by the tone of the cardiac nerves, that of the lower, idioventricular pacemakers is much less susceptible to such influences. If the center which dominates the heart action is reached and discharged by a premature extraneous impulse, its rhythmic impulse formation is disturbed. In experiments carried out years back[2-4] it was demonstrated that the duration of the "returning cycle"[5] after a response to a premature stimulus may greatly exceed the duration of the cycle of the natural rhythm. The retardation of the dominant pacemaker may extend over more than one cycle, indicating a temporary depression of its inherent rhythmicity as a result of an inhibitory effect of the premature extraneous impulse. This phenomenon, although substantiated in later experimental studies,[6-10] has not been given sufficient emphasis in the analysis of cardiac arrhythmias in clinical electrocardiography. It is the purpose of this report to present several clinical instances in which the phenomenon of the depressant effect of premature extraneous impulses upon the dominant pacemaker can be demonstrated and to point out its significance in understanding the mechanism of some cardiac irregularities.

Examples of depression of the S-A and A-V nodes are shown in Figs. 1 to 3; the details of the analysis are given in the legends and are indicated diagramatically in the two cases shown in Fig. 3. Fig. 1 illustrates instances of depression of the S-A node by auricular premature impulses followed by an escape of another pacemaker (Fig. 1,*a*) or of the A-V node (Fig. 1,*b*). In Fig. 1,*c*, cardiac standstill occurs repeatedly as a result of depression of both the primary and secondary pacemakers after salvos of auricular tachycardia. In Fig. 2,*a*, a nodal premature impulse reaches the sinus node in retrograde fashion. The ensuing competition of the depressed and slowly recovering sinus node with an escaping A-V nodal pacemaker is demonstrated by the appearance of fusion P waves. The same

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital Chicago.

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*Emil and Fanny Wedeles Fellow.

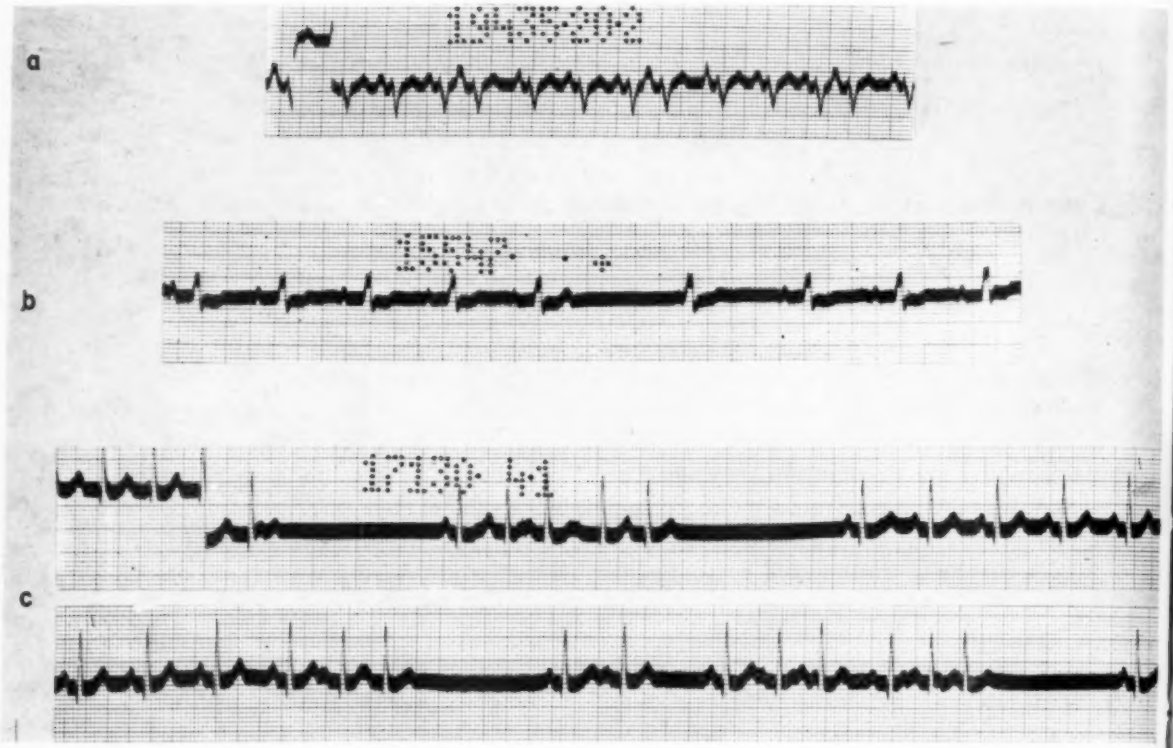

Fig. 1.—Depression of cardiac pacemakers by premature auricular impulses.

a, Lead II. "Shift of the pacemaker" following single auricular premature beats. Sinus tachycardia (rate 130); every fourth beat occurs prematurely due to auricular premature systoles with fixed coupling. The pause following the premature P wave is less than compensatory, the respective P-P intervals measure 0.08 to 0.10 second more than the sinus interval. In the middle part of the tracing (after the second and third premature beats) the postextrasystolic pause is terminated by a peaked and tall P wave, which resembles in its contour the premature P wave.

b, Lead II. Depression of the sinus node by a nonconducted auricular premature beat with escape of the subsidiary (A-V nodal) pacemaker. In the first half of the tracing regular sinus rhythm is seen at a rate of 83 (P-P interval 0.72 second). The T wave of the fifth ventricular complex is distorted by a superimposed premature, nonconducted P wave. The succeeding P-P interval measures 1.38 second, the respective R-R interval 1.26 second. The shortening of the P-R interval of the postextrasystolic beat to 0.08 second indicates an escape of the A-V nodal pacemaker at a rate of 47. The next beats are again of sinus origin (P-R 0.20 second); however, the slowing of the sinus pacemaker continues for two more cycles (P-P of 0.88 and 0.76 second), and the initial cycle length of 0.72 second is restored only with the last sinus interval of the record.

c, Lead I, a continuous record; the last beat of the upper strip is repeated as the first beat of the lower strip. There is depression of the primary and secondary pacemakers by short paroxysms of auricular tachycardia. Sinus rhythm with slight irregularity, corresponding to a rate of 94 to 100, is present in a group of beats at the end of the upper strip and continues at the beginning of the lower strip. This group of sinus beats is terminated by three successive auricular premature beats, the last of which (notch at the base of the descending limb of the last R wave) is nonconducted. The other groups seen in the record consist of one sinus beat followed by a single or by runs of varying numbers of auricular premature beats with irregular A-V conduction, exhibiting Wenckebach periods with evidence of concealed A-V conduction of some of the "nonconducted" impulses. These groups are separated from each other by periods of auricular and ventricular standstill. The interval of asystole measures 0.72 second (corresponding to a rate of 83) after a single premature beat (middle of lower strip) and 2.0 second (corresponding to a rate of 30) after six successive premature beats (middle part of upper strip). The long ventricular pause not only indicates that the S-A node was depressed but suggests that a normally acting secondary pacemaker in the A-V node was also depressed by the run of premature impulses occurring in rapid succession.

phenonemon, observed in another case where a long tracing was available, is seen in Fig. 2,*b*. Here, the spacing of the A-V nodal beats (Table I) suggests the presence of a permanently discharging (parasystolic) pacemaker in the A-V junction. Depression of the dominating sinus pacemaker by the prematurely occurring retrograde impulse, discharged by the parasystolic center, permits the reappearance of the latter in the long pause which follows the premature beat. Fig. 3 demonstrates how depression of a pacemaker may be due to a premature impulse conducted in a forward direction. Here, the dominating A-V nodal pacemaker is disturbed by conducted impulses from the slower S-A node (partial A-V dissociation). The inhibiting effect of these premature discharges upon impulse formation in the A-V node is evidenced by the transient prolongation of those automatic cycles which follow the successful or attempted (concealed)

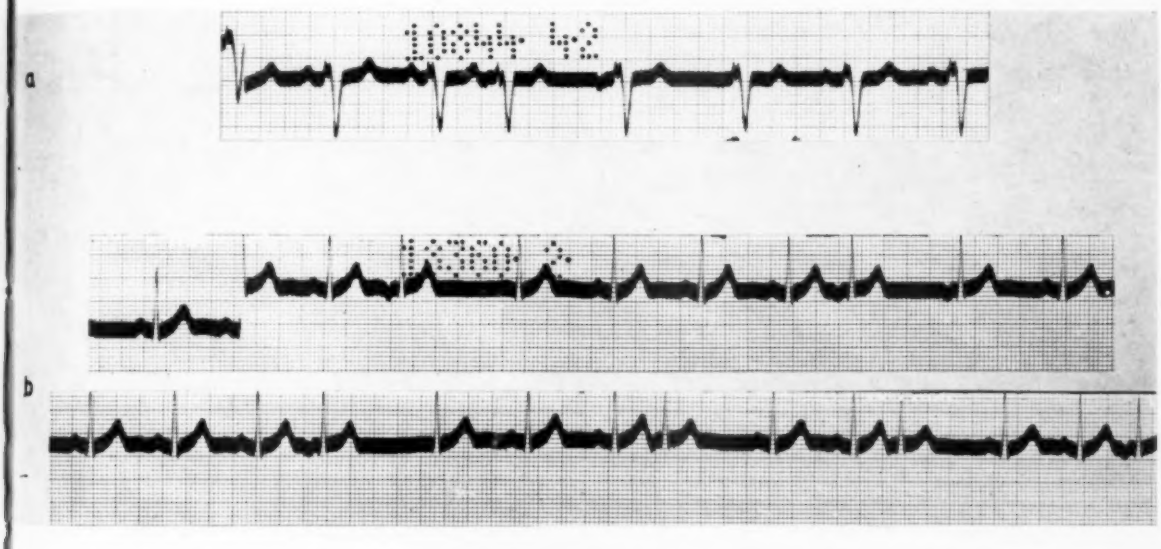

Fig. 2.—Depression of the sinus node by premature A-V nodal impulses with retrograde conduction. *a*, Lead II. Escape of an A-V nodal pacemaker during transient depression of the sinus node. Sinus rhythm is seen at the beginning of the record. Two upright P waves, occurring at an interval of 0.84 second (corresponding to a rate of 71), are followed by QRS complexes at a P-R interval of 0.16 second. The next QRS appears prematurely and is preceded at a distance of 0.14 second by a premature inverted P. The same shortened P-R appears to be associated with the next two P waves, which occur at an interval of 0.98 second (corresponding to a rate of 61). The first of them is inverted, indicating retrograde activation of the auricles; the second is intermediate in contour between the retrograde and the sinus P waves (fusion P). The following P wave is again upright; the respective P-R interval is 0.16 second; however, the P-P interval is still longer (0.88 second) than the sinus interval at the beginning of the tracing. The P-P interval of the last cycle is again 0.84 second, although the P wave is still slightly smaller in size.

b, Lead II. Continuous record. The last beat of the upper strip is repeated as the first beat of the lower strip. Measurements reveal a parasystole of A-V nodal origin with slight irregularity of the parasystolic pacemaker (Table I); the parasystolic beats appear in form of both premature systoles and escapes. Similar conditions are present as described for *a*. The upright (sinus) P waves are slightly irregular (rate 79 to 86); the corresponding P-R interval measures 0.14 second. Note that the A-V nodal premature systoles have a varying coupling and are preceded by a premature inverted P wave with shortened P-R interval. The beats following the premature beats are preceded by P waves which are either inverted or of a contour intermediate between the inverted and upright P waves and have a shortened P-R interval of varying duration. The ventricular complexes of these beats are of A-V nodal origin (corresponding to an average rate of 60); the auricular complexes of intermediate contour indicate fusion of the A-V nodal with the delayed sinus impulses.

A-V conduction of a sinus impulse and is responsible for the subsequent escape of the sinus node in the instance of Fig. 3,*a*.

DISCUSSION

The type of disturbance of the cardiac rhythm following a premature systole depends mainly on whether or not the dominant pacemaker is reached by the premature impulse. If the dominant pacemaker is not reached, the premature beat is either interpolated or, more often, followed by a fully compensatory pause. If, on the other hand, the premature impulse reaches and discharges the pace-

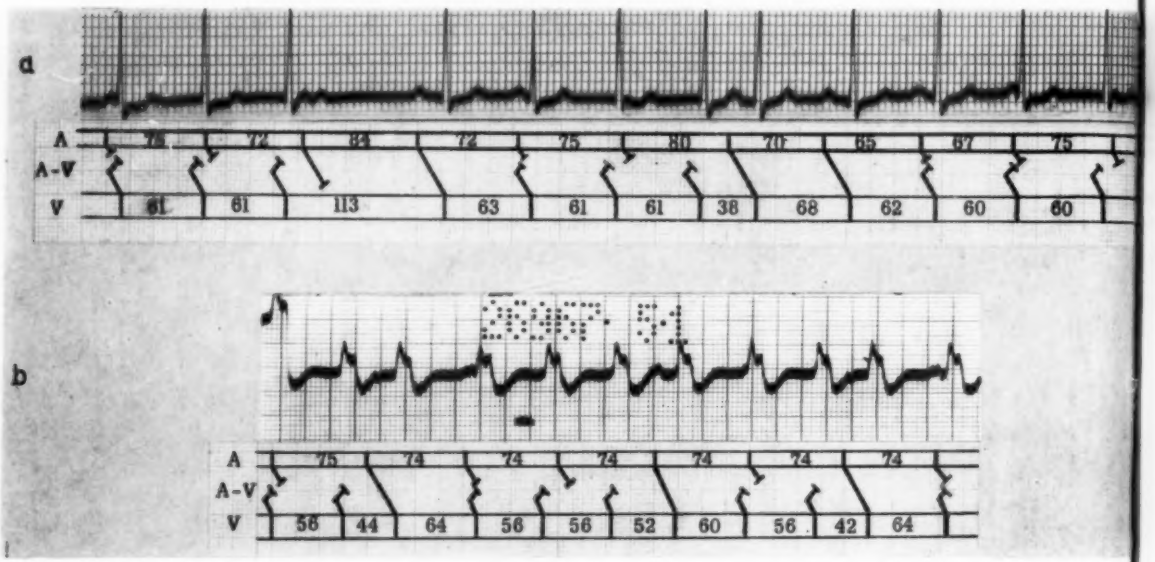

Fig. 3.—Depression of the secondary A-V nodal pacemaker by a sinus impulse (ventricular capture) in cases of partial A-V dissociation. The conventions in the diagrams below the tracings are those used customarily: *A-V* represents the spread of an impulse through the A-V junction between the auricles (*A*) and the ventricles (*V*); oblique lines at different angles indicate varying speeds of impulse conduction through the A-V junction; the short lines at right angles to the oblique lines indicate blockage of the impulse; varying lengths of the oblique lines, representing blocked impulses, indicate the varying distances to which the impulses penetrate into the A-V junction.

***a*, Lead II. Time lines 0.05 second. The auricular rate is irregular; the P waves are upright and identical in contour. A faster nodal pacemaker blocked in retrograde direction discharges at regular intervals of 0.61 second (rate 98) at the beginning and of 0.60 second (rate 100) at the end of the tracing. On two occasions, after the third and seventh ventricular complexes, the sinus impulse penetrates into the A-V junction and discharges the A-V nodal pacemaker prematurely. In the first instance it is blocked below the A-V nodal pacemaker (concealed conduction); in the second instance it gives rise to a ventricular capture (eighth ventricular complex). The beat following the premature discharge of the A-V nodal pacemaker by the sinus impulse occurs after an interval which is longer than the subsequent R-R interval between two A-V nodal beats and is assumed to represent a conducted beat. Regardless of whether this beat is a conducted sinus beat or an A-V nodal escape, the failure of the A-V nodal beat to appear at the expected time indicates a temporary depression of the A-V nodal pacemaker following its premature discharge by the sinus impulse.**

***b*, Lead I. Partial A-V dissociation due to A-V tachycardia with retrograde block. The supraventricular origin of the tachycardia in the presence of left bundle branch system block is evidenced by the identical contour of ectopic and conducted beats. The R-R interval, following the third, seventh, and tenth ventricular complexes (ventricular captures) is longer (0.60 to 0.64 second) than the other R-R intervals (0.56 second) which represent the regular A-V nodal rhythm at a rate of 107. The prolongation of the first automatic cycle following a conducted beat is due to a transient depression of the impulse formation in the A-V nodal pacemaker following its premature discharge by the sinus impulses, which are conducted to the ventricles.**

TABLE I. R-R INTERVAL OF BEATS OF A-V NODAL ORIGIN, ILLUSTRATED PARTLY IN FIG. 2,*b*
(ALL VALUES IN HUNDREDTHS OF A SECOND)

R-R INTERVALS IN LEAD II		R-R INTERVALS IN LEAD III*	
MEASURED	CALCULATED AS MULTIPLE OF 96-106	MEASURED	CALCULATED AS MULTIPLE OF 93.3-98
104	104 × 1	288	96 × 3
296	98.8 × 3	98	98 × 1
98	98 × 1	192	96 × 2
291	97 × 3	280	93.3 × 3
96	96 × 1	192	96 × 2
196	98 × 2	194	97 × 2
208	104 × 2		
212	106 × 2		

*Not illustrated.

maker, the premature beat is followed by a cycle which is longer than that of the natural rhythm without, as a rule, being fully compensatory. The lengthening of the returning cycle may be considerable and in many cases can hardly be explained entirely by the conduction time from the site of extraneous impulse formation to the site of the pacemaker.[4,8,9] Engelmann,[2] experimenting on the sinus venosus of the frog's heart in 1897, found an unexpected and marked slowing of the spontaneous rhythm following an induced systole and, dependent on the prematurity of the latter, even temporary standstill of the sinus. This observation was confirmed and extensively studied by other investigators[3,4,6-10] in experiments on the isolated heart and on the mammalian heart in situ. A depression of the spontaneous rhythmicity of the different pacemakers following their premature discharge was postulated as an important factor responsible for the lengthening of the returning cycle after the premature discharge of the pacemaker by the impulse of a premature systole. Lewis, in his experiments with White,[5] failed to find evidence that "extrasystoles by altering the rate of the dominant rhythm materially influence the length of the returning cycle." However, Lewis later[11] made the statement that "the depressant factor must be taken into account in analyzing clinical extrasystoles." Similarly, it was found that the depression of impulse formation by premature extraneous impulses may affect an idioventricular pacemaker. Actually, long before the depressant effect of premature ectopic impulses upon the S-A and A-V nodes was studied, slowing of the ventricles was shown to occur in experimentally produced A-V block when one or more impulses originating in the sinus node reached the ventricles[12,13] or when the idioventricular rhythm was temporarily interrupted by responses to a rapid stimulation of the ventricles.[4,14] The degree of inhibition of spontaneous impulse formation was found to be dependent on several factors. It increased in degree as the forced impulse became more premature.[2,3,6,8,9] A run of premature impulses was followed by greater inhibition than isolated premature impulses.[4,6,10,11,15] Furthermore, the depressant effect was more pronounced if the preparation exhibited a hypodynamic state of the cardiac muscle and a decline of spontaneous rhythmicity.[4,6,7,8]

These experimental results can be applied to the analysis of clinical arrhythmias like those presented in Figs. 1 to 3. Depression of the rhythmicity after a premature discharge by an extraneous impulse may affect the primary pacemaker (Figs. 1 and 2) as well as a hyperactive secondary center (Fig. 3). The long standstill of both auricles and ventricles seen in Fig. 1,*c*, would indicate that the activity of the whole system of cardiac pacemakers may be suppressed temporarily by a run of premature beats and prevent the escape of a lower center during a ventricular pause of 2 seconds. The occasional observation of depression of the sinus node following retrograde conduction to the auricles of nodal or ventricular premature beats in otherwise normal tracings speaks against Lewis's statement[11] that depression of this pacemaker is seen only "when, for various reasons, the heart is in the condition which has been termed hypodynamic." On the other hand, it has been our experience that a demonstrable depression of the A-V nodal pacemaker after a premature discharge like that shown in Fig. 3 is a rare phenomenon. On the contrary, more frequently in such instances of partial A-V dissociation, the first automatic cycle after a ventricular capture is found to be shortened by a few hundredths of a second. This shortening has been adequately explained[5,16,17] by a delay in conduction below the A-V nodal pacemaker affecting the premature impulse responsible for the ventricular capture. Thus, the duration of the first automatic cycle after the ventricular capture depends upon the balance of two opposite effects: (a) the depressant effect of the premature impulse which tends to lengthen the cycle and (b) its delayed conduction, below the site of the nodal pacemaker, which tends to shorten the cycle. In most instances the latter factor appears to be dominant and outweighs and completely masks the inhibiting effect. The balance of the two opposite effects may explain some irregularities observed by Lewis and White[5] in their studies on the effect of premature beats in A-V nodal rhythm.

Some of the factors which tend to enhance the depression of a pacemaker following premature beats may be recognized in our illustration. In Fig. 1,*c*, the pause succeeding a single auricular premature beat (middle of the lower strip) is only 0.20 second longer than the regular sinus interval of 0.60 second. The long periods of sinus standstill are seen to occur after runs of conducted and nonconducted premature auricular systoles. On the other hand, in Fig. 1,*b*, a single premature beat has a marked depressant effect on the sinus rate, which is not restored before the fourth succeeding cycle. Here, the marked effect might be ascribed to the short coupling of the ectopic impulse, which also accounts for its failure to be conducted to the ventricles. However, depression of the dominant pacemaker extending over several cycles can also be seen after single premature beats occurring in the middle of diastole (Fig. 2,*a*) and may permit escape of a slower center with ensuing competition of both pacemakers for the control of the heart, manifested by fusion beats (Fig. 2,*a* and *b*). If, as in Fig. 3,*a*, a nodal pacemaker is activating the ventricles, its premature discharge by a ventricular capture may be followed, during the time of its temporary inhibition, by another conducted sinus beat, which may be termed a sinus escape.[8,11]

The occurrence of aberrant auricular complexes following auricular premature beats is a well-known phenomenon. The fact that the aberrant P wave may be similar in contour to the premature one was explained by a postextrasystolic shift of the pacemaker[18] or by the assumption of an abnormal but similar pathway in the auricle taken by both the ectopic and postextrasystolic sinus impulse.[19] With respect to the analogous phenomenon occurring frequently after premature contractions of A-V nodal origin, reappearance of the ectopic center responsible for the premature beat in form of an escape seems more likely. Such an escape of a subsidiary pacemaker during the period of depression of the primary pacemaker was clearly demonstrated both in the experimental animal and in man.[7,18,20,21]

The appearance of a series of ectopic beats during the time of suppression of the primary pacemaker would suggest that the premature beat may exert a stimulating effect upon impulse formation in ectopic centers[18] in addition to its depressing effect upon the primary center. This assumption appears to be supported by the rather rapid rate of the escaping rhythm which, as in Fig. 2, may exceed the expected spontaneous rate of a subsidiary pacemaker. Such a double effect of premature impulse was also described by Miki and Rothberger.[8] Lewis[5,11] was of the opinion that in the normal heart premature beats exert a stimulating effect upon impulse formation in the S-A and A-V nodes in contrast to their depressing effect upon rhythms generated in the ventricles.

In some cases,[21,22] Figs. 291 and 292 the spacing of extrasystolic and escaping beats, their identical contour, and their fusion with sinus beats suggest the presence of a paraystolic pacemaker with "protection block" in the A-V junction. In our own observation (Fig. 2,*b*; Table I) slight deviations (±0.064 second) from the calculated parasystolic interval (0.996 second) can be explained if variations in conduction time from the A-V nodal pacemaker to the ventricles are taken into account.

The cause of the transient slowing of a cardiac pacemaker following a premature extraneous discharge remains a matter of speculation as long as the physicochemical processes responsible for the spontaneous heartbeat are unknown. A state of fatigue[4] or delayed recovery[10] due to the premature discharge and an impairment of reactivity[7] were suggested without convincing evidence. It would appear that beside these local events a neurogenic (reflex) effect mediated through the pressoreceptors could be operative. However, such an assumption is not in accord with the common observation of a fully compensatory pause following ventricular premature beats without evidence of slowing of the natural rhythm. Actually, the phenomenon of ventriculophasic sinus arrhythmia in A-V block[23,24] can also be observed in association with ventricular premature systoles[25] and would suggest that an acceleration rather than retardation of the sinus pacemaker may occur as a result of a premature systole with ventricular response. Furthermore, a neurogenic reflex slowing of the pacemaker was ruled out in the experiments where the depressant effect of premature impulses was demonstrated in the denervated heart.

Clinical Implications.—The Morgagni-Adams-Stokes syndrome can be due to attacks of ventricular tachycardia or fibrillation, to ventricular standstill following such paroxysms of tachycardia, or to transient asystole in cases of

A-V or S-A block.[26] Clinical examples of depression of an idioventricular rhythm by single or multiple premature ectopic beats leading to Morgagni-Adams-Stokes attacks have been reported.[27] Wenckebach and Winterberg[15] quote the unusual observation of an instance of incomplete A-V block where retardation or standstill of the ventricles was initiated by premature beats not of ectopic origin but transmitted from the sinus node during temporary restoration of A-V conduction. The slow onset and progressive acceleration of an idioventricular rhythm which becomes established after a period of ventricular standstill can be viewed as a manifestation of the phenomenon under discussion, viz., depression of the inherent rhythmicity of a pacemaker due to its discharge by another faster pacemaker; thus, Gaskell's rhythm of development may actually represent a process of gradual cessation of inhibition of a subsidiary pacemaker. Experimental evidence quoted above would suggest that no fundamental difference exists between the mechanisms underlying a posttachycardic and preautomatic pause, either of which, if of critical length, can produce the alarming clinical picture of the Morgagni-Adams-Stokes attack.

SUMMARY AND CONCLUSIONS

1. Electrocardiograms are presented demonstrating depression of the spontaneous rhythmic activity of different cardiac pacemakers (S-A and A-V node) by premature extraneous impulses.

2. This disturbance of rhythm is common when an ectopic impulse of auricular, A-V nodal, or ventricular origin reaches the sinus node and is partly responsible for the duration of the postextrasystolic pause.

3. The depressant effect is found less commonly when, in partial A-V dissociation, the A-V nodal pacemaker is discharged prematurely by a conducted sinus impulse. Its absence in such cases may be more apparent than real since the inhibitory effect of the sinus impulse upon the duration of the first automatic cycle may be masked by an opposite effect due to delayed conduction of the sinus impulse from the A-V nodal pacemaker to the ventricles.

4. During the prolonged cycles of the dominant pacemaker, following its premature discharge, escape of a subsidiary pacemaker and competition of both for control of the heart (fusion beats) may be observed. One such instance of sinus rhythm with A-V nodal premature systoles is shown where both the premature systoles and the subsequent escapes were actually due to the discharge of a parasystolic pacemaker in the A-V node.

5. In accordance with experimental data of the literature, the depression of a cardiac pacemaker was found to be more marked when its premature discharge occurred either early in its spontaneous cycle or repeatedly and in rapid succession. In contrast to some experimental findings, it is evident from the presented material that in the human heart the inhibiting effect is also exerted upon centers with higher spontaneous activity like the S-A node.

6. Gaskell's rhythm of development of a subsidiary pacemaker appears to be due to gradual cessation of inhibition of the latter after its continuous and relatively rapid discharge by extraneous impulses is over.

7. Transitory or permanent suppression of pacemakers with lower rhythmicity following single or multiple discharge by centers of high rhythmicity seems to be the underlying mechanism of ventricular standstill in certain clinical cases with Morgagni-Adams-Stokes attacks.

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FACTORS INFLUENCING THE T WAVE OF THE ELECTROCARDIOGRAM

II. Effects of Drinking Iced Water

Charles V. Dowling, M.D.,* and Herman K. Hellerstein, M.D.**

Cleveland, Ohio

RECENT animal experiments in which intracavitary and extraventricular (epicardial) leads were employed[1] have clarified the effects of heating and cooling the endocardium and epicardium. Changes in the T wave were produced by changing the rate and order of endocardial-epicardial laminar repolarization. Negative T waves occurred where the exploring electrode subtended areas which had relatively or absolutely retarded repolarization; positive T waves occurred where the exploring electrode subtended areas which had relatively or absolutely accelerated repolarization. In the present report we have been interested in exploiting similar thermally induced changes for the purpose of learning more about the form and genesis of the T wave in human beings.

In 1923, Wilson and Finch,[2] using the three standard bipolar limb leads, gave about 600 c.c. of iced water to six normal human subjects and took records before and at frequent intervals after its ingestion. They observed transiently increased negativity of the T wave in Leads II and III. This "primary" change was attributed to the retarded rate of repolarization induced by cooling the posteroinferior surface of the apex of the left ventricle, which had been in contact with the distended fundus of the stomach. Drinking equal quantities of warm lemonade had no effect on the form of the electrocardiogram.

The present investigators felt that if this classic experiment of Wilson and Finch were repeated with unipolar limb and multiple precordial leads, it could be demonstrated more conclusively that some of the bioelectric phenomena recorded from the heart of the dog and other species are operative in the human heart as well. It was decided, moreover, that the results could be subjected to a more quantitative kind of analysis by determining the ventricular gradients before and after the ingestion of iced water.

MATERIAL AND METHODS

The experimental subjects were divisible into four broad groups on the basis of their electrocardiographic patterns and clinical history: (a) six normal resident

From the Department of Medicine, Western Reserve University School of Medicine, and the University Hospitals, Cleveland.

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*Resident in Medicine, University Hospitals of Cleveland, Ohio. At present Postdoctorate Research Fellow of the National Institute of Health, United States Public Health Service, and Assistant in Medicine in the Department of Medicine, New York University College of Medicine.

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physicians, (b) eleven hypertensive patients with signs of left ventricular hypertrophy, (c) nine patients with old anterior myocardial infarction, and (d) eight patients with old posterior myocardial infarction.

At the time of the experiment, Leads I, II, III, aV_R, aV_L, aV_F, V_1, V_2, V_5, and V_7 or V_8 were recorded. Control tracings were taken with the subjects in the recumbent position. Immediately after the rapid ingestion of approximately 800 c.c. of iced water, and for several five-minute intervals after that, serial electrocardiograms were taken, all with the subjects in the control position. At a later date, four normal subjects ingested 800 c.c. of tepid tea (38° to 40° C.), and serial electrocardiograms were similarly recorded. In these control experiments, slight change in the electrical position of the heart occurred, but no primary alterations of the T wave.

The ventricular gradient was determined by the projection and planimeter method of Wilson,[3] before and after ingestion of iced water, for those subjects who, by inspection, showed significant alteration in the T wave. Each gradient was analyzed according to the criteria set forth by Ashman.[4-9]

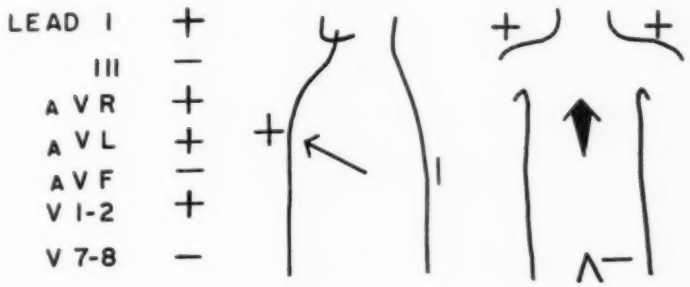


Fig. 1.—Effect of drinking iced water on the T wave. (+) indicates absolutely more positive or relatively less negative T waves; (−) indicates absolutely more negative or relatively less positive T waves. The T vector is represented as an arrow which becomes directed away from the region of delayed repolarization (posterior wall of the heart being cooled by iced water).

RESULTS

A total of thirty-four experiments was done. By inspection of the records, those were called positive (and chosen for gradient analysis) which showed an appreciable relative or absolute negativity of the T wave in Leads III and aV_F after the ingestion of iced water without significant change in the electrical position of the heart. Thus, the records of twenty-two subjects were projected for gradient analysis: five of six normals, five of eleven hypertensive patients with left ventricular hypertrophy, six of nine patients with anterior myocardial infarcts, and six of eight patients with posterior myocardial infarcts.

In addition to the effects noted in Leads III and aV_F, other significant alterations were observed consistently in the positive reactors: The T wave in Leads I, aV_R, aV_L, and in the right-sided precordial leads tended to become relatively or absolutely more positive, while in the left posterolateral chest leads and Leads II, III, and aV_F, the tendency was for the T wave to show a decreased positivity or increased negativity (Fig. 1). In Figs. 2 to 11, representative examples of these

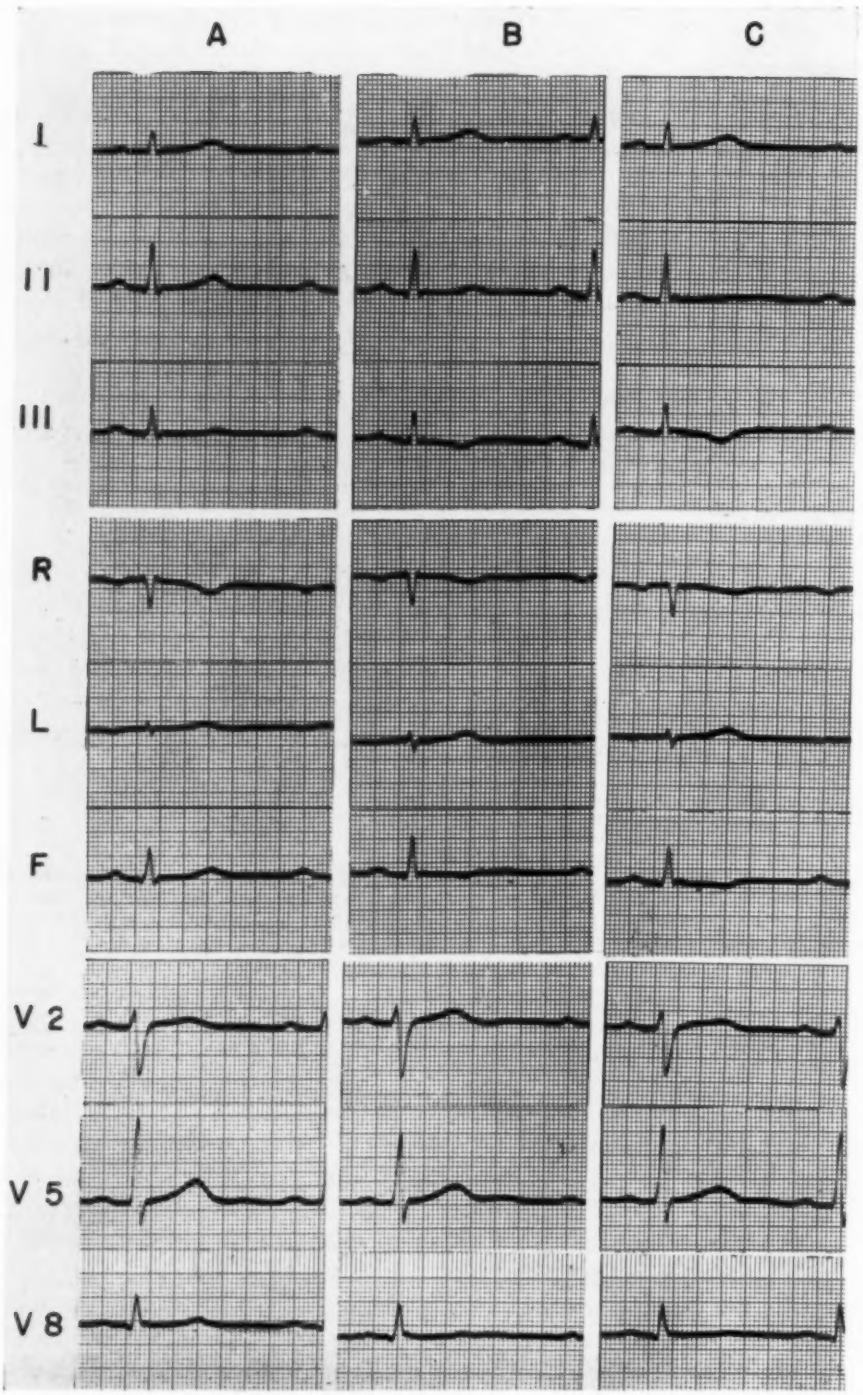
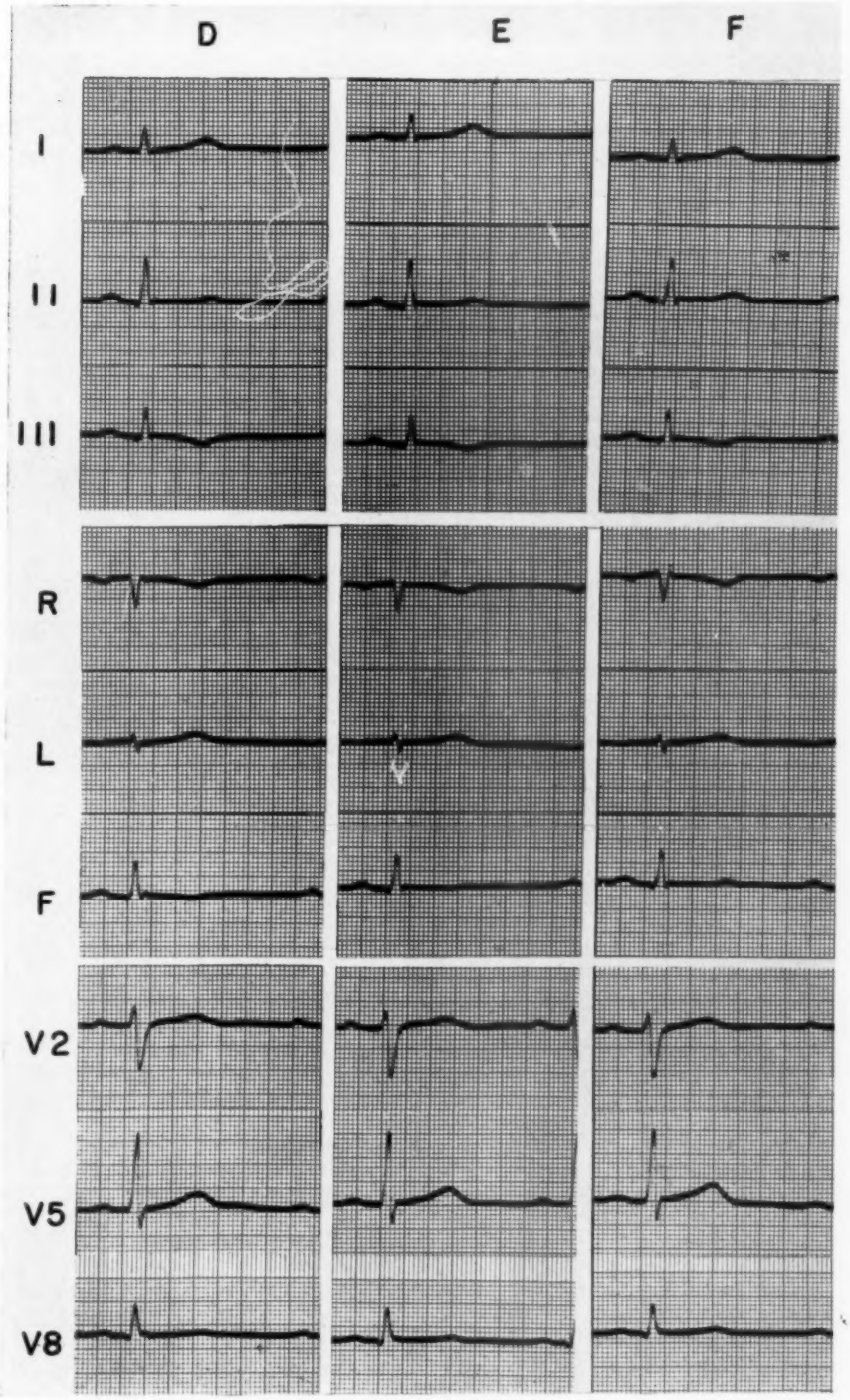


Fig. 2.—Effect of drinking 800 c.c. of iced water; paper speed 50 mm. per second. Additional normal physician. Serial electrocardiograms: *A*, control; *B* to *F*, 1, 2, 5, 10, and 15 minutes after iced water. Serial records (*A* to *C*) show progressive T-wave inversion in aV_F and Lead III, flattening of



T in Leads II, V_5, and V_8, and decreased negativity of T in V_2 and aV_L. At the end of 15 minutes recovery is not complete, since T is inverted in Lead III and is low in aV_F. Note that a negative T wave occurs in Lead III when aV_F is negative (*B*, *C*), when aV_F is nearly isoelectric but aV_L is more positive (*D*, *E*), and when aV_F is positive but aV_L is more positive (*F*).

changes in the four groups are presented. One patient, however, showed a serious deviation (Case 5, left ventricular hypertrophy group, Fig. 8). In this case the T wave in aV_F became more positive, and in aV_L more negative; the changes in the T wave possibly were primary since the ventricular gradient decreased 40 per cent, while $\hat{A}_{QRS}$ decreased 23 per cent. The angle between

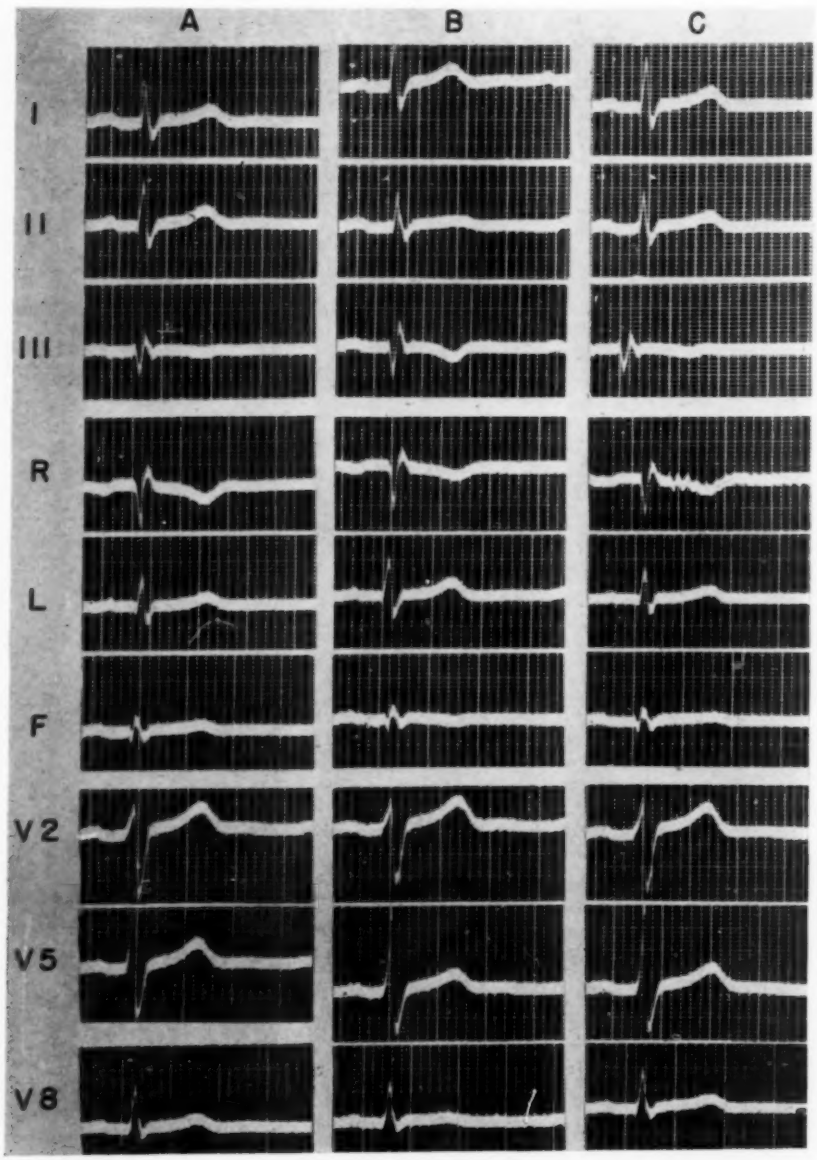


Fig. 3.—Case 3, normal group. Thirty-year-old physician with incomplete right bundle branch block and no other evidence of heart disease. Effect of drinking 800 c.c. of iced water; paper speed 50 mm. per second. Column *A* is control, *B* and *C* are 1 and 5 minutes later. Note the inversion of the T wave in aV_F and Lead III, diminution of T in Leads II, V_5, and V_8, decreased negativity of T in aV_R, and increased positivity of T in Leads I, aV_L, and V_2.

$\hat{A}_{QRS}$ and $\hat{G}$ remained unchanged. The possibility of cooling of the anterolateral wall of the left ventricle due to a diaphragmatic hernia was excluded by roentgenographic studies.

There was no significant change in the heart rate in most of the subjects. Occasionally a transient increase of 5 to 10 beats per minute was observed. The Q-T interval was infrequently prolonged after the ingestion of iced water from 0.02 to 0.04 second.

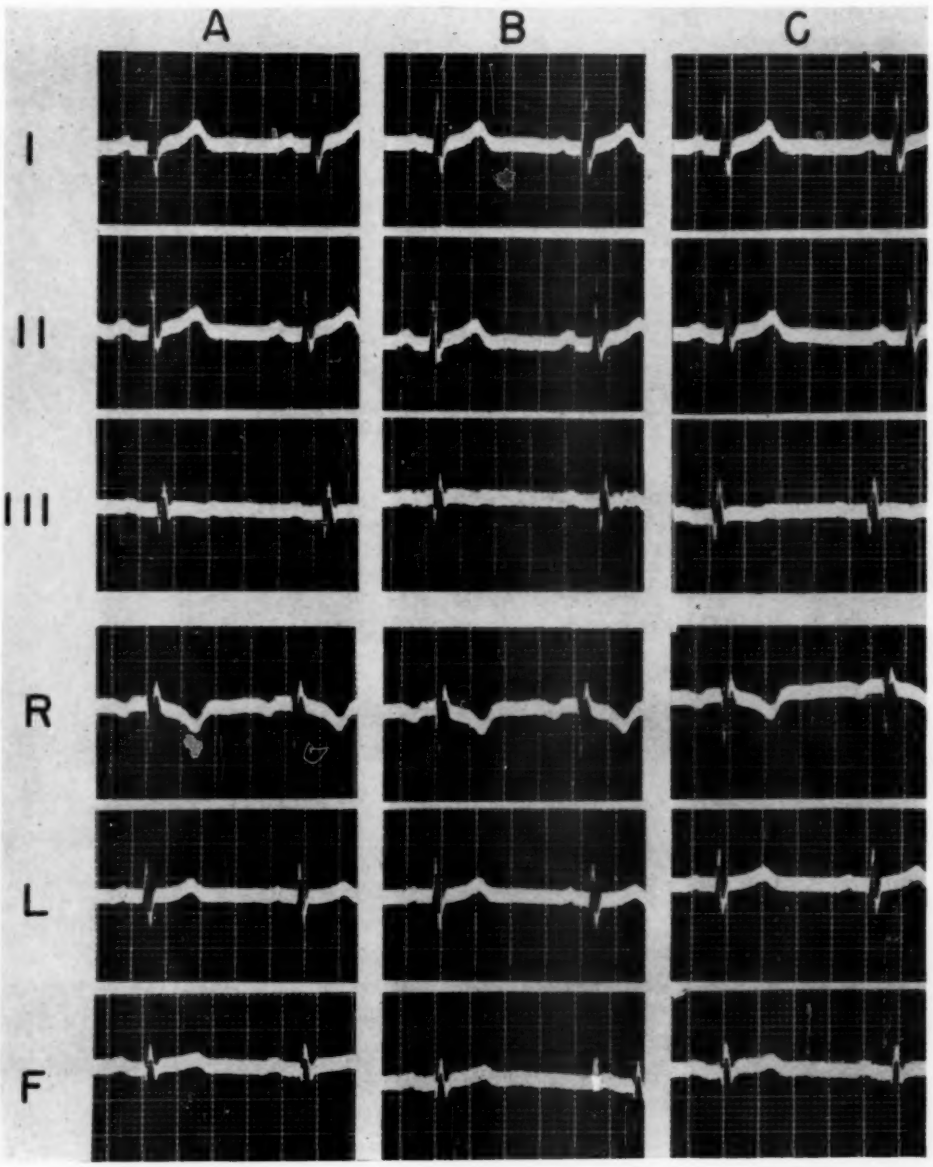


Fig. 4.—Same physician as in Fig. 3. Note lack of effect of drinking 800 c.c. of tepid tea (body temperature). *A*, control; *B* and C are 2 and 5 minutes later.

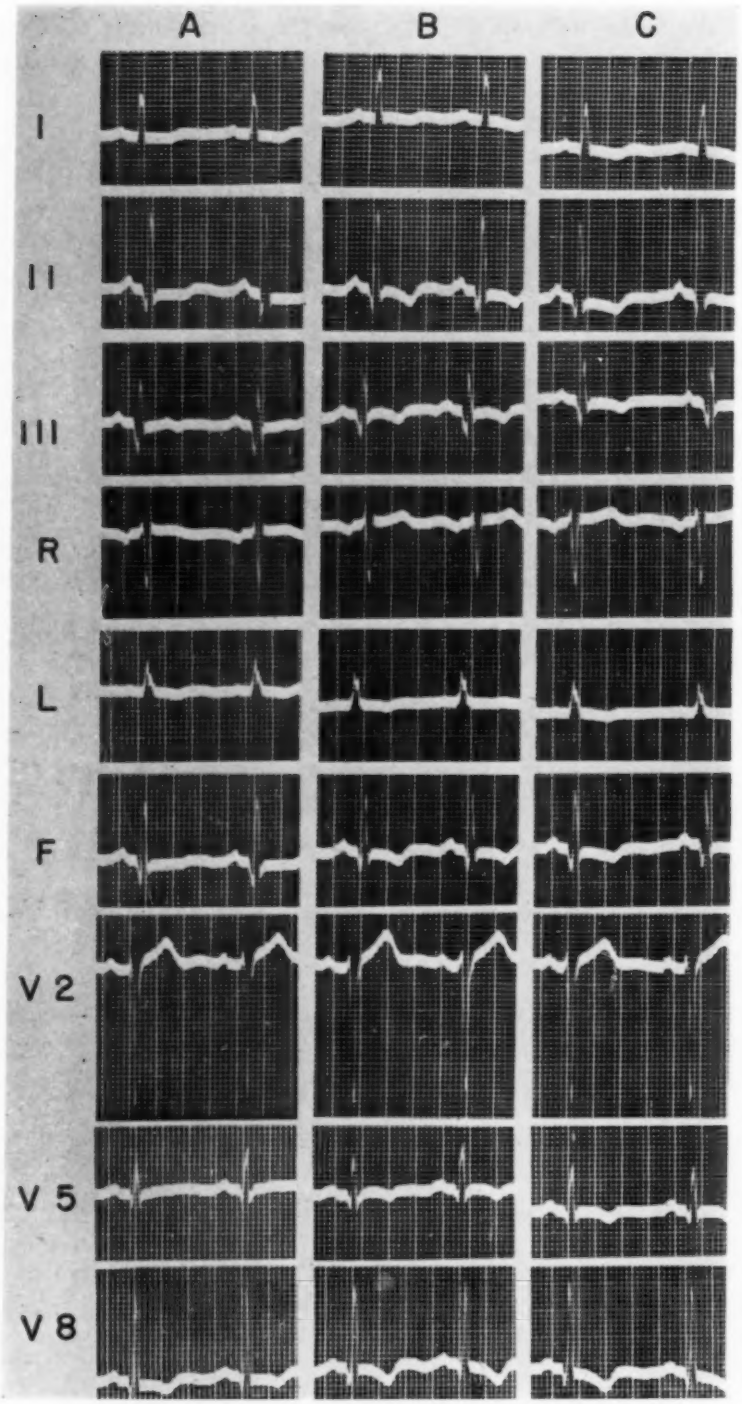


Fig. 5.—Old posterior myocardial infarct (Case 3). Column *A* is control, and *B* and *C* are 1 and 5 minutes after drinking 800 c.c. of iced water. Note inversion of T in Leads II, III, aV_F, V_5, and V_8. T in aV_R became more positive.

In only one instance was there even a suggestion that angina pectoris had been produced by the rapid drinking of iced water. A patient with signs of an old posterior myocardial infarct experienced mild discomfort beneath the midsternum, which subsided spontaneously within a few seconds. Records made at this time showed no evidence of acute coronary insufficiency.

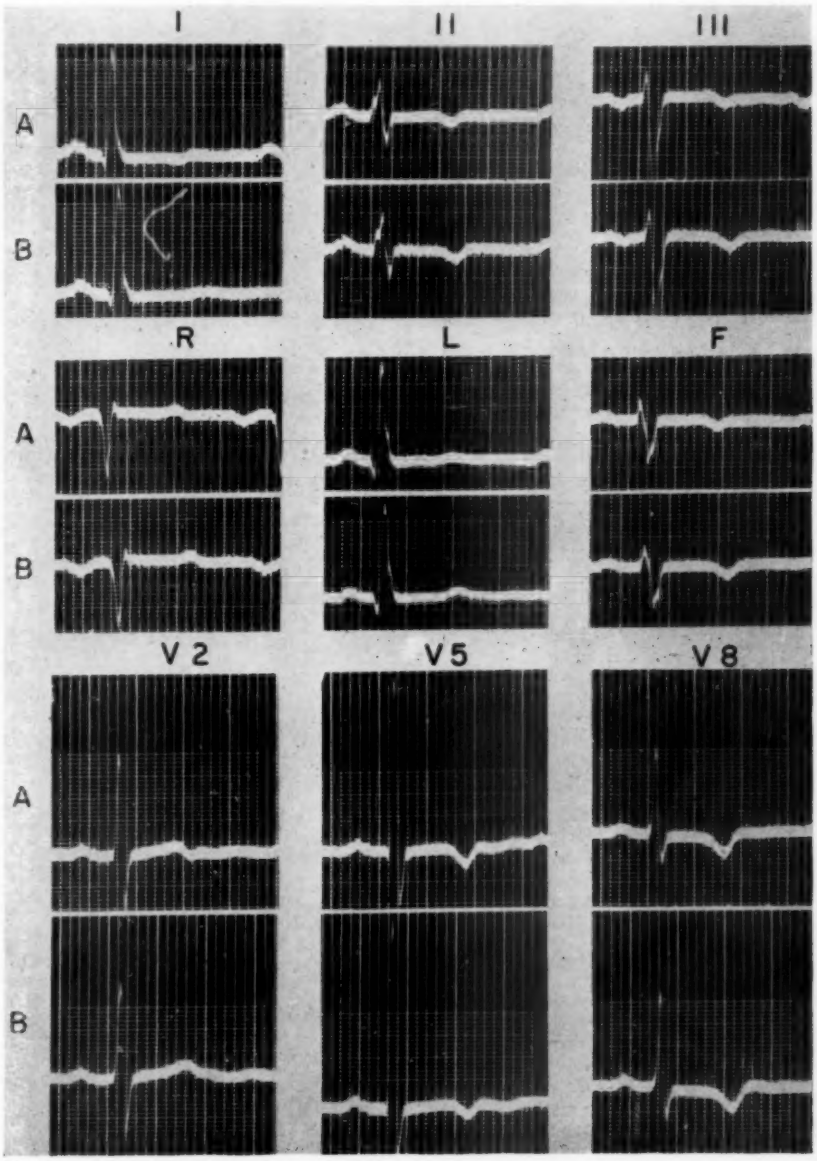


Fig. 6.—Left ventricular hypertrophy (Case 2). Paper speed 50 mm. per second. *A*, control *B*, 2 minutes after 800 c.c. of iced water. Note increased inversion of T in Leads II, III, aV_F, and V_8; T in V_2 became upright and in V_5 less inverted. T is taller in aV_L. The Q-T interval is prolonged by 0.04 second.

Analysis of the twenty-two sets of ventricular gradients finally yielded a total of eighteen subjects whose electrocardiograms after the ingestion of iced water showed primary[13] T-wave changes: five normals, four with left ventricular hypertrophy, five with anterior infarcts, and four with posterior infarcts. Table I is a summary of the effects of the experimental procedure on the ventricular gradient of those showing primary T-wave changes. (Values for the anatomical

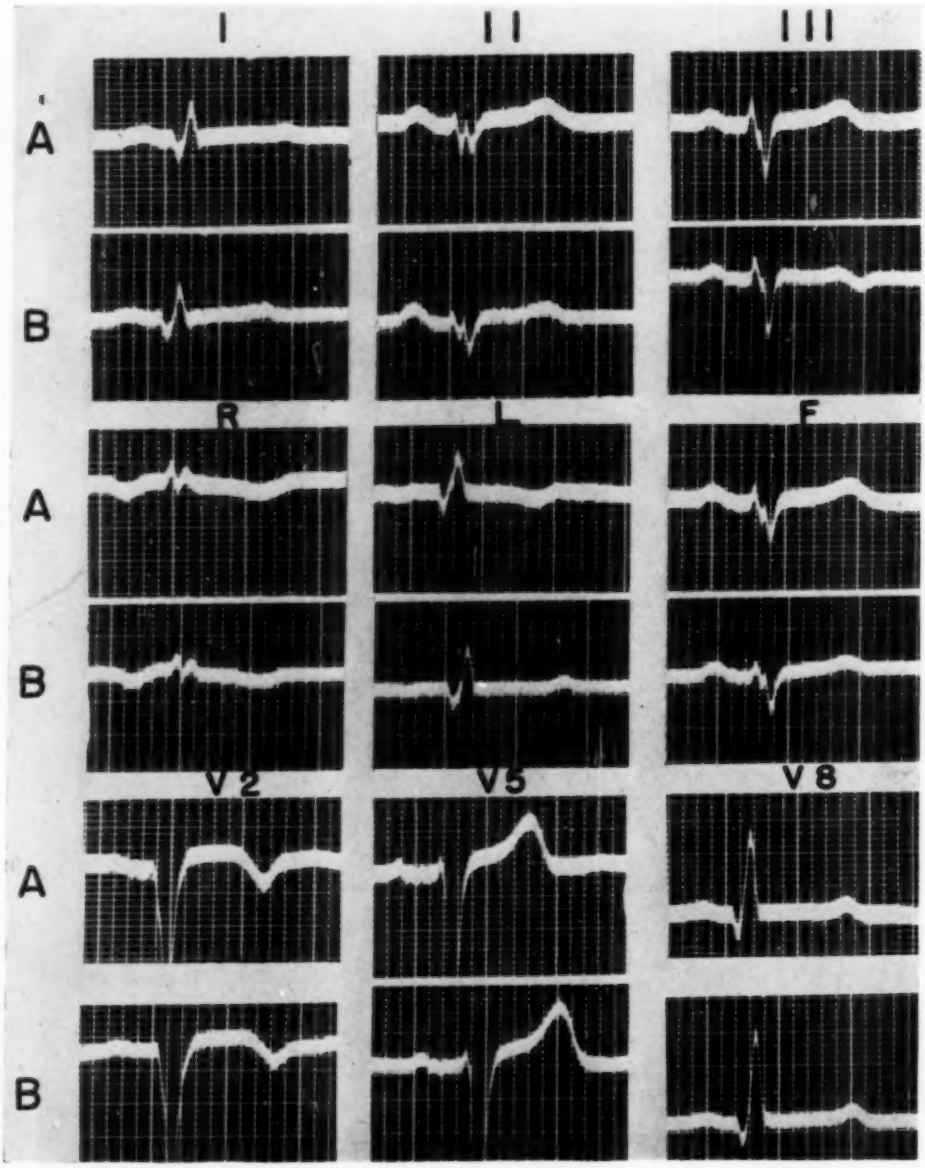


Fig. 7.—Old anterior myocardial infarct (Case 2). Paper speed 50 mm. per second. Effect of 800 c.c. of iced water. *A* is control; *B*, 2 minutes after iced water. Note inversion of T in Lead III, lowering of T in aV_F; T in aV_L became upright, and T in aV_R and V_2 less negative.

axis $\hat{H}$ were estimated by the method of Ashman[11] which employs the standard bipolar limb leads and is useful for normal hearts only.[12])

The paths of the terminus of $\hat{G}$ after the ingestion of iced water are plotted in Fig. 9. There was a general tendency in all groups for $\hat{G}$ to move counterclockwise toward the first and second sextants. This is the same region to which

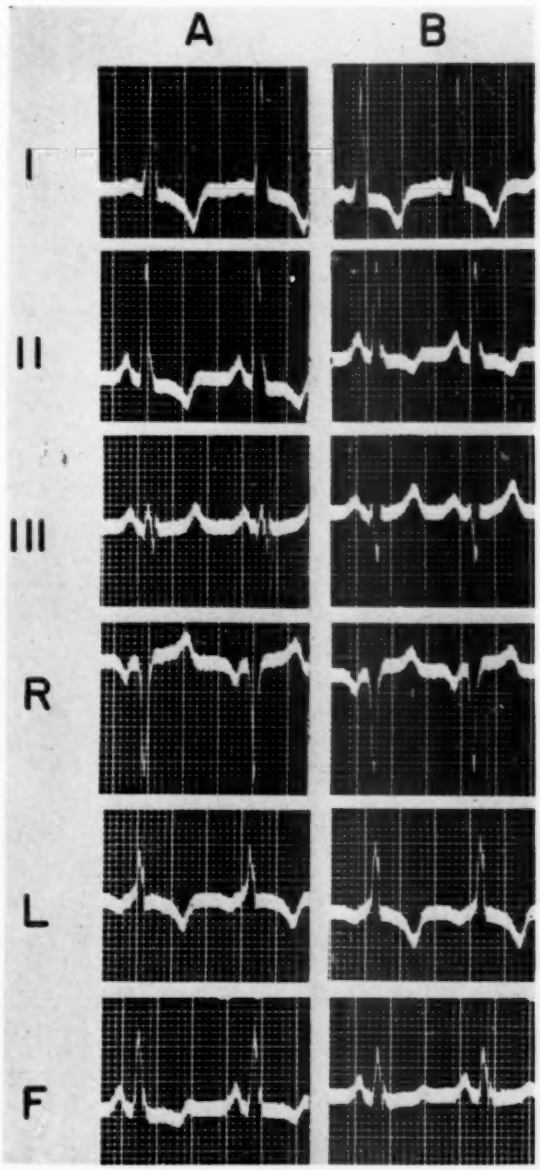


Fig. 8.—Left ventricular hypertrophy (Case 5). Atypical effect of drinking iced water. The T wave became upright in aV_F and more inverted in aV_L. There was some change in electrical position, but the angle between $\hat{A}_{QRS}$ and $\hat{G}$ remained unchanged. $\hat{G}$ decreased 40 per cent; $\hat{A}_{QRS}$ decreased 23 per cent. Discussed in text.

TABLE I. SUMMARY OF THE EFFECT OF DRINKING ICED WATER ON THE VENTRICULAR GRADIENT OF EIGHTEEN PATIENTS IN WHOM PRIMARY T-WAVE CHANGES WERE PRODUCED

CASE NUMBER	MAGNITUDE*		AXIS		ANGLE BETWEEN $\hat{A}_{QRS}$ AND $\hat{G}$	PER CENT CHANGE		ANGLE OF G WITH H†	
	$\hat{A}_{QRS}$	$\hat{G}$	$\hat{A}_{QRS}$	$\hat{G}$		$\hat{A}_{QRS}$	$\hat{G}$	OBSERVED	CALCULATED
Normals									
1. Control	5.5	15.8	−7	10	17.0	49	12.7	15	15
Cold water	8.2	17.8	−1	−1	0.0			26	14
2. Control	4.8	13.5	74	52	22.0	16.7	−27.4	3	8
Cold water	5.6	9.8	68	44	24.0			11	5.5
3. ‡Control	1.3	12.5	−27	20	47.0	−33	−21.6	20	9.0
Cold water	1.0	9.8	−13	−13	0.0			38	4.0
4. Control	9.3	19.5	47.5	23.2	24.3	−10.8	−15.0	6.8	5.0
Cold water	8.3	16.5	37.5	5.8	31.7			34.2	1.0
5. Control	4.5	16.5	62.5	61.5	1.0	4	−34.6	6.5	3.0
Cold water	4.7	10.8	62.0	39.6	22.4			0.4	10.0
Left Ventricular Hypertrophy									
1. Control	9.1	1.3	−45	−124	79	−6	290		
Cold water	8.5	5.8	−42	−90	48				
2. Control	16.0	15.5	−31	−59	28	6.3	8.4		
Cold water	17.0	16.8	−26	−43	17				
3. Control	8.3	2.2	−35	0	35	3.6	86		
Cold water	8.6	4.1	−30	3	33				
4. Control	7.5	5.0	−5	3	8	6.7	90		
Cold water	8.0	9.5	−20	−51	31				
5. §Control	14.0	5.0	31	90	59	−23	−40		
Cold water	10.8	3.0	10	68.5	58.5				
Anterior Myocardial Infarct									
1. Control	1.2	1.6	−77	−107	30	16.7	37		
Cold water	1.4	2.2	−53	−72	19				
2. Control	3.4	7.3	−62.5	62.5	125	5.9	−52		
Cold water	3.6	3.5	−76	−4	72				
3. Control	5.8	4.7	35	21	14	−3.5	6.4		
Cold water	5.6	5.0	30	−37	67				
4. Control	4.2	2.7	87.5	116	28.5	14.3	−70		
Cold water	4.8	0.8	85.0	194	109				
5. Control	6.1	14.2	−4	42	46	−14.8	−40		
Cold water	5.2	8.5	−16	28	44				

TABLE I.—CONT'D

CASE NUMBER	MAGNITUDE*		AXIS		ANGLE BETWEEN $\hat{A}_{QRS}$ AND $\hat{G}$	PER CENT CHANGE		ANGLE OF $\hat{G}$ WITH $\hat{H}$†	
	$\hat{A}_{QRS}$	$\hat{G}$	$\hat{A}_{QRS}$	$\hat{G}$		$\hat{A}_{QRS}$	$\hat{G}$	OBSERVED	CALCULATED
Posterior Myocardial Infarct									
1. Control	2.5	2.7	72	−15	87	−60	56		
Cold water	1.0	4.2	31	−51	82				
2. Control	7.5	5.5	17.8	0	17.8	10.7	27.3		
Cold water	8.3	7.0	17.8	−11.5	29.3				
3. Control	5.8	2.2	37	8.2	28.8	3.5	64		
Cold water	6.0	3.6	27	−33.5	60.5				
4. Control	1.4	0.6	66	30	36	36	550		
Cold water	1.9	3.9	45	− 8	53				

*The magnitude of $\hat{A}_{QRS}$ and $\hat{G}$ is expressed in 4 microvolt-second units.

†$\hat{H}$ is estimated by the method of Ashman, and the "calculated" angle of $\hat{G}$ with $\hat{H}$ obtained from Ashman's table.[7]

‡Case 3 in the normal series has incomplete right bundle branch block. Discussed in text.

§Data of Case 5, left ventricular hypertrophy group, are discussed in text.

the manifest gradiant G sweeps when there is local ischemia involving that portion of the ventricular muscle which is ordinarily irrigated by the right coronary artery (posterior wall[10]).

Fig. 10 is a composite graph showing the effect of cooling represented as a vector quantity.[12] These vectors were constructed as follows: The ventricular gradients before and after cooling were determined in the usual manner; a parallelogram was then completed and the gradient after cooling expressed as a resultant of two forces, one the control gradient before iced water, the other a theoretical force representing the "cooling effect" (Fig. 10,*A*). The grouping of the majority of these "cooling effect" vectors around minus 90 degrees is quite striking and had been noted previously by Wilson.[12] This effect is what might be expected if the greatest cooling was of the epicardial surface of the diaphragmatic wall of the heart. With the exception of two patients with left ventricular hypertrophy, the remainder are more or less in line, with a tendency for the normals and those with anterior wall infarcts to be distributed from minus 90 to minus 120 degrees, and for the patients with left ventricular hypertrophy and posterior wall infarcts to lie in the first sextant.

Since the "cooling effect" vector is around minus 90 degrees, it is not surprising that if the control gradient pointed in the general direction of minus 90 degrees, drinking iced water increased the magnitude of $\hat{G}$; if the control gradient approached plus 90 degrees, $\hat{G}$ was reduced (Table I and Fig. 9). This may be stated in another way: Drinking iced water caused a decrease in the magnitude of the ventricular gradient if the controls were located in the fifth and sixth

sextants (there is only one exception, normal group, Case 1); drinking iced water caused an increase in the magnitude of the gradient if the controls were located in the first and second sextants.

COMMENTS AND DISCUSSION

The effects of cooling (short of the production of tissue injury and death) on the electrical behavior of cardiac muscle and other excitable tissues have been well demonstrated to comprise primarily an increase in the duration of the excited state, or equivalently a deceleration of the recovery or repolarization process.[1] Since the ST-T complex is a record of this stage of regression, it is here that one sees most strikingly the alterations produced by cooling. The results of such

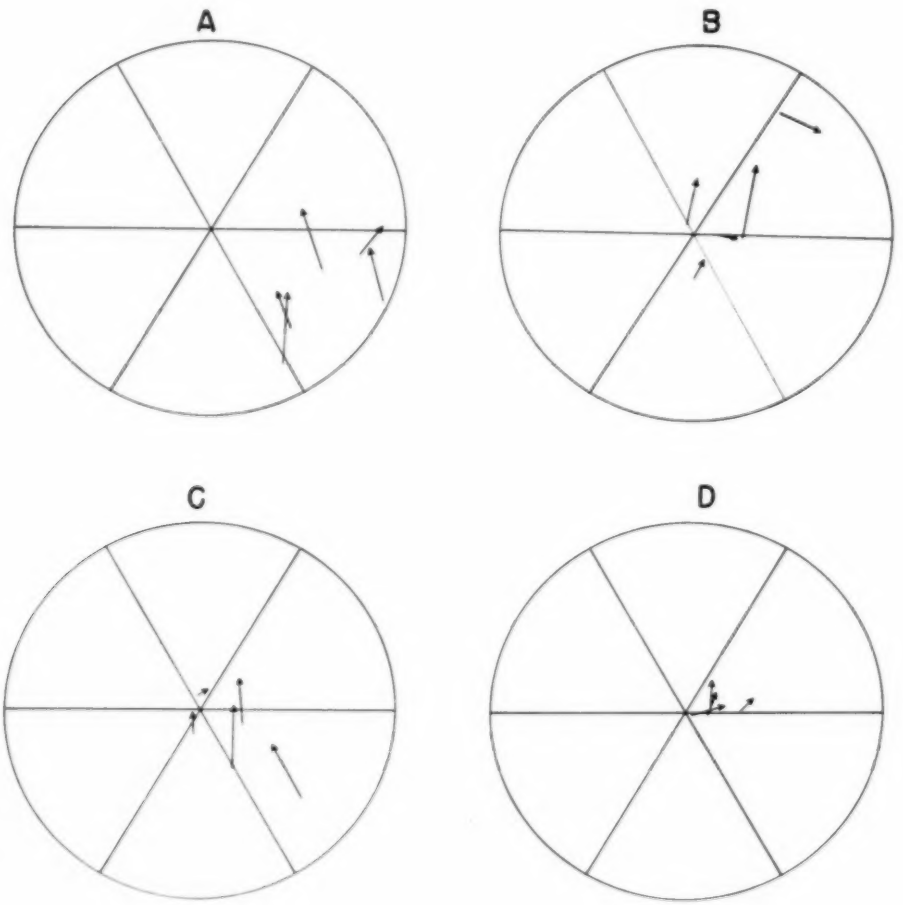


Fig. 9.—Path of terminus of $\hat{G}$ after the ingestion of 800 c.c. of iced water. *A*, Normals. $\hat{G}$ decreased in all but one case. *B*, Left ventricular hypertrophy. $\hat{G}$ increased in all but one case; control $\hat{G}$ of the latter was situated in the fifth sextant. *C*, Anterior myocardial infarct. $\hat{G}$ decreased in those cases in which the effect was close to minus 90 degrees. Two cases (1 and 3) increased. *D*, Posterior myocardial infarct. $\hat{G}$ increased in all cases. Note the general tendency in all groups for $\hat{G}$ to move counterclockwise toward the first and second sextants.

experiments have been readily explained by a logical extension of the classical membrane theory as applied to a heart immersed in an extensive conducting medium.[1]

The normal time course of repolarization of the ventricular myocardium may be represented by a vector, with positive head and negative tail, oriented in an endo-epicardial direction, which is an expression of the recovery process in the average element of muscle.[10] Although recovery begins at the epicardial surface, it consists of a receding wave of negativity or an advancing wave of positivity traveling toward the endocardium, whose electrical behavior therefore is that of a positive wave front advancing from endocardium to epicardium, thus the direction and sense of the vector.[1]

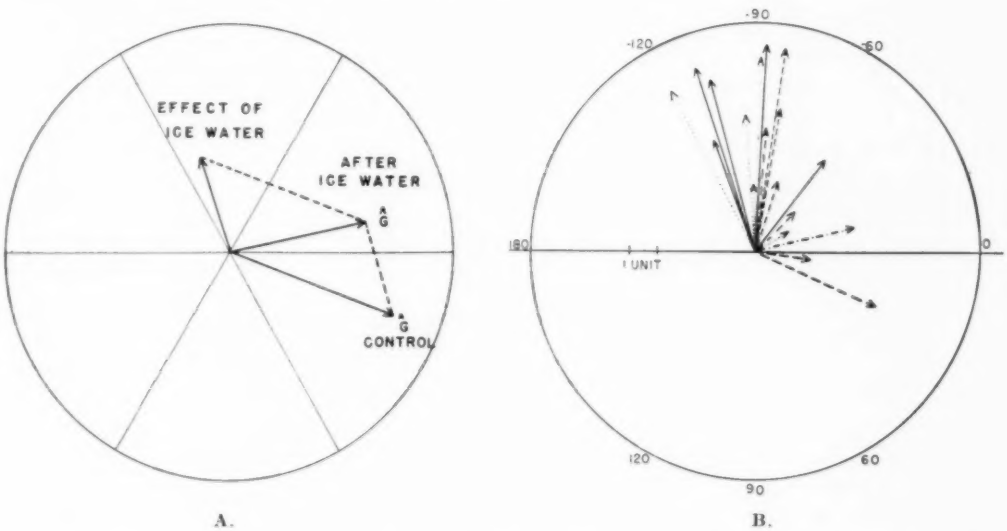


Fig. 10.—*A*, Method of showing the effect of cooling represented as a vector quantity (Case 3, normal series). *B*, Composite graph showing the cooling effect in eighteen cases. Solid lines = five subjects, normal house officers; broken solid lines = four subjects with left ventricular hypertrophy; dotted lines = five subjects with anterior myocardial infarcts; broken solid and dotted line = four subjects with posterior infarcts. Discussed in text.

For purposes of discussion, the muscle mass of the ventricle may be represented by the diagram shown in Fig. 12, in which the endocardial-epicardial direction of normal repolarization gradient is indicated by arrows at *A*, *B*, *C*, and *D*. An electrode placed over any point on the epicardium will be dominantly influenced by the electrical forces operative immediately beneath it, and to a lesser extent by all other forces having a component in a plane at right angles to the plane in which it lies. Using conventional electrocardiographic polarity, then, a positive T wave will be inscribed, which is in reality a resultant of myriad simultaneously acting electrical forces, with contributions—some directed oppositely, and, therefore, negative—from the region of *C* particularly. If heat is applied at *A* in diagram 1, repolarization will be accelerated in the subepicardial muscle in that area, and the magnitude of the *A* vector of repolarization will increase (diagram 2); T will become more positive in a unipolar lead from the

warmed epicardium and less positive (even frankly inverted) in a lead from the immediately subjacent endocardium[1] and in an epicardial lead from point *C* on the opposite wall. Cold, which causes a retardation of the recovery process, will have opposite effects (diagram 3): the *A* vector will tend to develop an epicardial-endocardial direction, i.e., to decrease in magnitude. If *A* is the seat of infarction, local cooling increases the magnitude of the *A* vector (diagrams 4 and 5). On the other hand, if the contralateral wall is the seat of infarction, cooling at *A* (diagrams 6 and 7) may reverse the *A* vector sufficiently to counterbalance the force from the contralateral wall and produce isoelectric or even positive T waves in the precordial leads. This actually occurred in the group with anterior myocardial infarcts. Thus, one abnormality may tend to annul another. The alterations of the T wave in the above situations are but a special case of the general rule that the algebraic addition of electrical forces having a component normal to the plane of the recording electrode will result in an increase or decrease in the areas of the various deflections of the electrocardiogram.

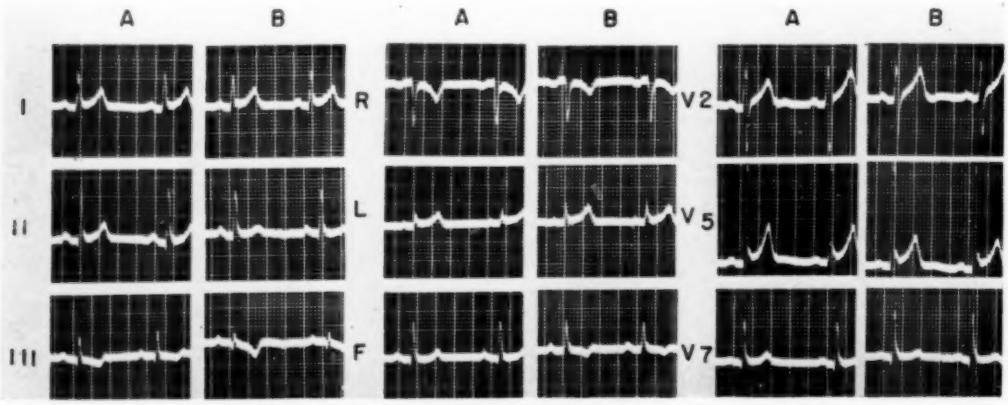


Fig. 11.—Case 4, normal group. Effect of drinking 800 c.c. of iced water. Column *A* is control, and Column *B* is 5 minutes after iced water ingestion. Both primary and secondary T-wave changes occurred. Discussed in text.

The magnitude and sign of the change depend on the spatial orientation to the exploring electrode of the positive and negative poles of the vector representing the force; if the positive pole faces the electrode, the area of some portion of the electrocardiogram will become more positive or less negative (the deflection affected depending on the phase of the heart's electrical cycle during which the force acts); if the negative pole faces the exploring electrode, a decrease in positivity or an increased negativity will result. Experimental electrocardiography, particularly that in which intracavitary electrodes have been used, abundantly illustrates this rule.[1]

In the present experiments, the T vector after iced water ingestion is considered to point toward the left arm, less toward the right arm, and away from the left leg, in a projection on a frontal plane. In the sagittal plane, the T vector points ventrad, since the T wave becomes inverted in tracings from the posterior chest and positive in anterior leads (Fig. 1).

The present series of iced water experiments in human beings seems then to be the counterpart of the work done with animals in which an intracardial lead has been employed. Lead aV_F, which most closely approximates a direct lead from the cooled area, together with Leads II and III and the unipolar leads from the left posterolateral chest show a diminution of the T wave; Lead aV_R, which often resembles an intracavitary or endocardial lead, and Leads I, aV_L,

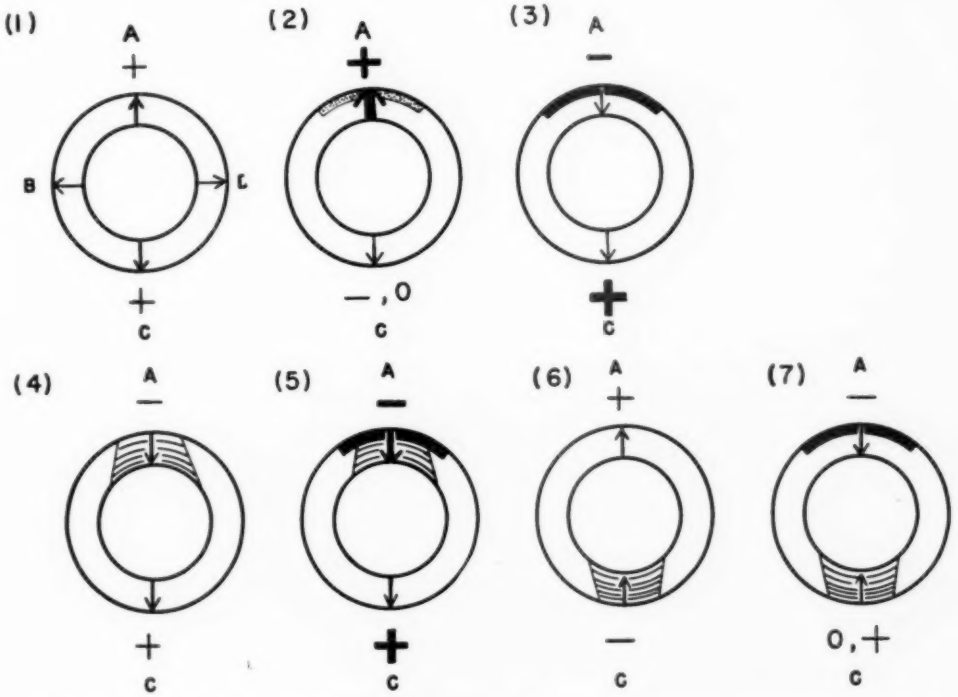


Fig. 12.—Diagrammatic representation of the effect of thermal changes in various locations on the T wave in normal hearts[1,2,3] posterior wall infarcts,[5] and anterior wall infarct.[7] The figures *1*, *4*, *6* are controls for *2* and *3*, *5*, *7*, respectively. The blackened area in figures *3*, *5*, *7* locates the zone of laminar epicardial cooling produced by the ingestion of iced water. The stippled area in figure *2* indicates the region heated. The plus sign means positive T waves, zero isoelectric T waves, and the minus sign negative T waves. The vectors of repolarization are represented as arrows, pointing away from areas in which the duration of the excited state is greatest. Cooling produced negative T waves in the region cooled and relatively or absolutely positive T waves on the contralateral wall. Discussed in text.

and the right-sided precordial leads show an increase in the amplitude (and area) of T. One would assume that cooling subendocardial muscle layers would result in the production of changes directed oppositely to those engendered in this group of experiments;[1] actually, such effects have been noted by one of us (HKH) during catheterization studies in human beings.

About the failure of some subjects to show little or no primary T-wave change, we can only speculate. Several possible explanations suggest themselves: (1) The distended fundus of the stomach was too far distant from the heart tc have any cooling effects on it; (2) the stomach emptied too quickly; (3) the heart was too well insulated to be affected thermally by cold gastric contents (this may

be the explanation for the failure of a patient with chronic pericarditis—not included in this series— to show significant changes); (4) the area cooled may have been so small in relation to the total electrically effective area (or so inaccessible to the exploring electrodes employed) that the electrocardiographic alterations resulting from local cooling were not gross enough to be detected. This situation may have obtained in some of those with left ventricular hypertrophy and could be the reason, at least in part, for the relatively small number of positive reactors in this group; (5) changes in QRS and T, attendant on physical displacement of the heart by the distended fundus of the stomach (secondary T-wave changes), may have obscured any primary changes in T due to local cooling; and (6) the area cooled may have consisted of dead muscle, so that it could be considered electrically inert. Such may have been the case in patients with old posterior infarcts. Parenthetically, there was no correlation between the electrical position of the heart in the control records and the degree of changes after iced water ingestion.

In most cases, the differentiation of primary from secondary T-wave changes, i. e., of alterations of T due to gradient affecting the duration of the excited state from those attributable to differences in the form of QRS induced by changes in the position of the heart in the thorax, presented no difficulties. Two empirical observations assured us in many instances that unequivocal primary T-wave changes had occurred in both normal and abnormal hearts; the first was that frequently marked changes in T wave were unaccompanied by any discernible alterations of QRS; second, it was often noted that maximal changes of T did not occur immediately, when the stomach was presumably the most distended, but only after a few minutes. Analysis of the ventricular gradient, however, as has been shown, yielded evidence on a more objective and more quantitative level concerning the nature of the T-wave changes.

In some instances, combinations of secondary and primary T-wave changes seem to have occurred (Fig. 11). The attempt in these instances to separate quantitatively the change in T into these two components proved to be a problem in analysis that was often impossible of solution except in a very gross and approximate way. Not even the ventricular gradient method is precise enough to enable one to accomplish such a fractionation. Case 4 of the normal group demonstrates this point well (Fig. 11). After iced water, the heart is more horizontal; a part of the change in the ventricular gradient can be ascribed to this. Since the greater horizontality seems to be associated with little or no rotation of the ventricles about their longitudinal axis, the difference between the $\hat{A}_{QRS}$ change of 10 degrees and the $\hat{G}$ change of 17.4 degrees, or 7.4 degrees, might be ascribed to the cooling. However, empirically, we know that primary changes have taken place, viz., although the amplitude of aV_F has decreased, the net value of QRS is positive and the T wave has become negative. In a previous study[1] it was clearly demonstrated that negative T waves occurred where the exploring electrode subtended areas which had relatively or absolutely retarded repolarization. In spite of the positional change, the left leg was still facing the epicardium of the left ventricle, and normally a positive T wave should be inscribed.[1]

The limitations of the ventricular gradient in this regard are obvious when one considers that what is analyzed by this technique is the projection onto a plane of forces that actually are defined in three dimensions. If the only displacement that occurred were the result of rotation of the heart on an anteroposterior axis, i.e., in the frontal plane, then secondary changes could be separated more or less quantitatively from the total effect, since such displacement of itself would result in changes neither in the magnitude of $\hat{A}_{QRS}$ and $\hat{G}$ nor in their angular relationship to one another or to the anatomical axis $\hat{H}$. Thus primary changes could be assayed with a fair degree of accuracy. Rotation on a longitudinal or transverse axis, however, is another matter. In the first place (particularly in enlarged hearts) the anatomical axis cannot be established with any degree of accuracy.[12] Second, although it should be possible, theoretically, with the aid of special leads and application of the principles of solid geometry and vector analysis to determine the magnitudes and solid angles of the spatial vectors, S $\hat{A}_{QRS}$ and S $\hat{G}$, and the effects on their frontal projections of rotation along any axis, universally acceptable analytical methods have not yet been developed. The work of Grant[14] is particularly promising in this regard. It hardly needs mentioning that rotation taking place on two or more axes simultaneously would introduce even greater difficulties. All of the above notwithstanding, however, we do know that because of the angular relationship to one another of the spatial vectors H, S $\hat{G}$ and S $\hat{A}_{QRS}$, as calculated by Ashman,[7] movement around a longitudinal (base-apex) or transverse axis should produce larger angular changes, in the frontal projection, of $\hat{A}_{QRS}$ than of $\hat{G}$. Therefore, if the angular change of $\hat{G}$ exceeded that of $\hat{A}_{QRS}$, this difference was interpreted as indicative of a primary change.

Throughout our study, and that of Wilson and Finch,[2] the primary T-wave changes have been attributed to the retarded rate of repolarization of the posteroinferior surface of the left ventricle, in contact with the distended fundus of the stomach. The problem arises, particularly in patients with old posterior myocardial infarcts, of whether if the cooled wall is a dead wall, any changes other than those due to changes in heart position or to change in the conducting medium should occur. The occurrence of primary T changes in such cases indicates that some muscle in the posterior wall has survived.

The conclusion that the primary T-wave changes are due to actual cooling of the epicardial surface locally is not necessarily correct. Some other factors which may have been involved include: impaired coronary flow due to nervous reflexes originating in the stomach, coronary vasoconstriction and myocardial ischemia due to the transmitted effect of cold, and cold inhibition of some restorative chemical or physicochemical process. The absence of significant changes in the Q-T interval is not incompatible with the concept that actual cooling had been produced. In animal experiments on the exposed heart, local epicardial application of saline solution which is 35 to 36° C. will invert the T waves without significant Q-T changes; whereas cooling with iced water prolongs the Q-T interval about 50 per cent above control values.

SUMMARY

The electrocardiograms of thirty-four subjects were recorded before and at frequent intervals after the ingestion of 800 c.c. of iced water. By analysis of ventricular gradients before and after cooling, it was determined that primary T-wave changes were produced in five of six normals, four of eleven patients with left ventricular hypertrophy, five of seven with old anterior myocardial infarcts, and four of seven with old posterior infarcts. No deleterious effects were observed. Maximal changes in the electrocardiogram occurred within five minutes following ingestion of iced water and subsided completely within twenty-five minutes. In control experiments, 800 c.c. of tea at body temperature were ingested without significant change.

Primary T-wave changes occurred according to the following pattern: increased negativity or decreased positivity of the T wave in aV_F, Lead II, Lead III, and the left posterolateral chest leads; increased positivity or decreased negativity occurred in aV_R, aV_L, and the right-sided precordial leads.

The spatial relation of the exploring electrodes to the posterior heart, whose repolarization has been altered by cooling, is used to account adequately for the changes in the T wave.

The effect of cooling is represented as a vector quantity which tended to be grouped around minus 90 degrees on the triaxial reference system. This localization supports the concept that the T-wave changes observed are due to the delayed repolarization of the posterior wall of the heart, induced by the ingestion of iced water.

The ingestion of iced water causes a change in the direction and magnitude of the ventricular gradient; the effect of cooling is generally in a direction of minus 90 degrees; the magnitude is decreased if the control gradient is located in the fifth or sixth sextants and increased if originally in the first or second sextants.

We are deeply indebted to Dr. R. Ashman for his advice and assistance in this study, and particularly for suggesting the method for analyzing the effect of cooling.

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THE Q-T INTERVAL OF THE ELECTROCARDIOGRAM IN ACUTE MYOCARDITIS IN ADULTS, WITH AUTOPSY CORRELATION

I. Wilson Gittleman, M.D., M.S. (Med.), Louisville, Ky., M. C. Thorner, M.D., Beverly Hills, Calif., and George C. Griffith, M.D., Pasadena, Calif.

CARDITIS is the most frequent manifestation of rheumatic fever and is most often insidious and subclinical.[27] Believing that laboratory aids in the diagnosis of rheumatic fever currently used have been disappointing in determining when the rheumatic inflammatory process has begun or has ceased, Taran[22,23] studied the duration of electrical systole (Q-T interval), both absolute and relative to diastole, of fifty children with acute rheumatic carditis and fifty children during a long period of quiescence following acute rheumatic fever. He concluded that the duration of electrical systole, both absolute and relative to diastole, is significantly prolonged in all cases of acute carditis. The prolongation was found to be a function of the severity of the carditis and not of the cardiac rate.

The majority of physiologic studies indicate that disturbance in time relationship of systole and diastole is a manifestation of impaired function of the myocardium. Wiggers and Clough[26] found that the period of systole is of longer duration in functional cardiac disorders. They further stated that, when more blood returns to the ventricle, it responds by expelling more blood not only by a greater number of ejection periods, but also by a greater relative duration of each systole. Concerning this mechanism, Lombard and Cope[13] stated that the duration of systole is influenced so largely by the quantity of venous blood supplied to the heart that this factor may disguise the effect produced by the condition of the heart muscle. Katz[12] believes the duration of systole in the diseased heart as compared with the normal heart would give a method of determining the functional integrity of the myocardium. Fridericia[10] concluded that in man an abnormal increase in the duration of systole is indicative of myocardial weakness.

There is considerable variation of opinion, however, among clinicians and physiologists regarding the clinical importance of the measurement of the duration of electrical systole (Q-T interval). Ashman and Hull[4] stated that measurement of electrical systole may give valuable information regarding the degree to which the myocardium is being affected in diphtheria and in acute rheumatic carditis. Cheer[6] reported that electrical systole is greatly increased in heart failure, irrespective of etiology, and that an increased electrical systole may indicate a disturbance in cardiodynamics which might well be formed before clinical evidence is available. In a later study, Cheer and Dieuaide[8] found that relative

From the Department of Medicine (Cardiology), School of Medicine, University of Southern California, and the Los Angeles County Hospital, Birmingham Veterans Administration Hospital, and Wadsworth Veterans Administration Hospital, Los Angeles.

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prolongation of the Q-T interval in cardiac insufficiency seems to be of myocardial origin. Again, they found that in cardiac failure resulting from various causes electrical systole is abnormally prolonged. However, they stated that no direct relation exists between the degree of heart failure and the value of K,* but relative prolongation of Q-T is present in earliest recognizable cases of myocardial insufficiency. Furthermore, they stated that electrocardiographic abnormalities such as prolonged conduction time and ventricular preponderance do not obviously affect the value of K, nor is any correlation between K and the size of the heart seen. Robb and Turman[15] believe that the Q-T duration seems to be directly related to metabolism, presumably cardiac cellular metabolism. Taran,[21,23] as noted above, stated that the Q-T interval, both absolute and relative to diastole, is significantly prolonged in all cases of carditis, and that this prolongation is a function of the severity of the disease and not of the cardiac rate.

On the other hand, White and Mudd[25] reported the Q-T interval to be of apparently little or no clinical value. They found no prolongation in patients with structural cardiac defects. In functional cardiac disturbances, they found a prolonged Q-T interval only in paroxysmal tachycardias or disorders causing a marked widening of the QRS complex.

The above-mentioned physiologic and clinical evidence presented the problem of ascertaining the corrected Q-T intervals in adults who died of acute myocarditis, also the problem of comparing the findings of patients with acute rheumatic myocarditis with the findings of patients with acute nonrheumatic myocarditis. To ascertain this information for diagnostic and prognostic purposes, the following study was made.

METHOD

A survey was made of all the patients over 21 years of age with autopsy diagnoses of acute myocarditis at Birmingham and Wadsworth Veterans Administration Hospitals and the Los Angeles County Hospital from 1941 to 1948. Only those cases were accepted which presented microscopic evidence of extensive myocarditis, which had not received digitalis for four weeks prior to the time electrocardiograms were taken, and which had electrocardiograms technically satisfactory for measurement. Fifty-one cases of acute myocarditis were collected, fourteen cases of which were rheumatic; the remainder were nonrheumatic.

As additional evidence, though it is admitted that it is less satisfactory, the literature was carefully examined for all autopsied cases of acute myocarditis with electrocardiograms. The above criteria were again used. Twenty-eight such cases were collected, none of which had rheumatic etiology.

The constants according to Bazett,[5] Ashman,[3] and Fridericia[10] were obtained for all of the electrocardiograms. Also the ratio $\frac{\text{Q-T}^{\dagger}}{\text{T-Q}}$ was ascertained in all

*K refers in their paper to the constant derived from Bazett's[5] formula, $\text{Q-T} = \text{K}\sqrt{\text{R-R}}$.

†$\frac{\text{Q-T}}{\text{T-Q}}$ is the ratio of electrical systole to diastole.

cases. When serial electrocardiograms were available, a study was made to determine whether there was any relationship between the constants and the $\frac{\text{Q-T}}{\text{T-Q}}$ ratio and the course of the disease.

In this study, Bazett's constant is noted Q-T_B, Ashman's as Q-T_A, and Fridericia's as Q-T_F.

FORMULAS

The lack of agreement upon a satisfactory formula is shown by the multiplicity of formulas available in the literature. Lombard and Cope[13] ascertained the Q-T interval in recumbent patients to be 0.105 R-R + 0.2010 for men and 0.065 R-R + 0.2478 for women. Both Fenn[9] and Smely[19] determined $\text{Q-T} = 0.39\sqrt{\text{R-R}}$. Savilahti[16] concluded that for both sexes $\text{Q-T} = 52 - \frac{\text{rate}}{5}$ for rates under 120 and $\text{Q-T} = 40 - \frac{\text{rate}}{10}$ for rates over 120. Fridericia stated his formula as $\text{Q-T} = 8.22\sqrt[3]{\text{R-R}}$. Schlomka and Raab[17] modified Fridericia's formula as follows: $\text{Q-T} = 7.95\sqrt[3]{\text{R-R}}$ for young people and $\text{Q-T} = 8.25\sqrt[3]{\text{R-R}}$ in aged people; Bazett[5] concluded $\text{Q-T} = 0.37\sqrt{\text{R-R}}$ for men and $0.40\sqrt{\text{R-R}}$ for women. Adams[1] postulated Q-T = 0.1536 R-R + 0.2462 for men and 0.1259 R-R + 0.2789 for women.

It will be noted that, in all the above formulas, the normal is stated but the range of normal is not. Without the upper limit of normal stated, the formulas are of little clinical value. Using Bazett's formula, Cheer and Li[7] found $\text{Q-T} = 0.374 \pm 0.0012\sqrt{\text{R-R}}$ for men and $\text{Q-T} = 0.388 \pm 0.0015\sqrt{\text{R-R}}$ for women. The American Heart Association,[14] using Bazett's formula, accepted the upper limits of normal as 0.392 for men and 0.440 for women. Commenting on the above formulas, Ashman and Hull[4] stated:

> ". . . other formulae have been proposed but Bazett's comes closer to the facts than the others. Yet this formula gives values which average too low for males, and which are too low for females when the heart is rapid and too high when the heart is slow."

Further, Ashman[2] believes:

> ". . . the cube root, square root and straight line formulae proposed by Fridericia, Bazett and Adams are incorrect. Bazett's formula . . . gives values which are appreciably too low at short cycle lengths and too high at the long cycle. Fridericia's formula using a K of 7.95 proposed by Schlomka and Raab for young adults gives values which are much too high when the heart is rapid and too low when the heart is slow. Adams' formula is still less applicable."

Ashman introduced an entirely new formula: $\text{Q-T} = \text{K} \log [10\ (\text{C} + \text{k})]$; $\text{C} = \text{R-R}$; $\text{k} = 0.07$. The upper limits of normal for K are 0.410 for men and 0.420 for women. Though our study is of adults only, and consequently no values for children were considered, it is to be noted for later reference that Ashman gave 0.405 as the upper limit of normal for children.

Various studies have been made to determine the range of the Q-T interval in normal adults. All of them were made using Bazett's formula. Viscidi and Geiger[21] examined the electrocardiograms of 500 unselected adults and found 17.0 per cent were above the upper limit of normal as set down by the American Heart Association. Shipley and Hallaran[18] found the range of Q-T in 200 normal adults between 0.337 and 0.443 for men and 0.380 and 0.456 for women. Stewart and Manning,[20] studying the electrocardiograms of 500 RCAF airmen, found 39.4 per cent above the upper limit of normal as stated by the American Heart Association, and 2 per cent above 0.440. Graybiel[11] studied the electrocardiograms of 1,000 healthy young aviators and found the range of Q-T between 0.300 and 0.590.

For this study, the formulas of Bazett,[5] Fridericia,[10] and Ashman[3] were compared. Using Bazett's formula, $Q\text{-}T = K\sqrt{R\text{-}R}$, K (designated in this study as $Q\text{-}T_B$) $= \dfrac{Q\text{-}T}{\sqrt{R\text{-}R}}$ The upper limit of normal for this formula was accepted as 0.392 for men and 0.440 for women as denoted by the American Heart Association.[14] Also, since Bazett's formula is so extensively used today, the upper limit of normal as determined by Shipley and Hallaran[18] was also used (0.433 for men, 0.456 for women). Despite the fact that no upper limit of normal for Fridericia's constant was given, his figure of 8.22 for normal is used. The formula is $Q\text{-}T = K\sqrt[3]{R\text{-}R}$ and therefore K (designated in this study as $Q\text{-}T_F$) $= \dfrac{Q\text{-}T}{\sqrt[3]{R\text{-}R}}$. This formula has been included because of the belief that it may be a very valuable formula once the upper limit of normal is determined. Using Ashman's formula, $Q\text{-}T = K \log [10\ (R\text{-}R + 0.07)]$, K (designated as $Q\text{-}T_A$) $= \log \dfrac{Q\text{-}T}{[10\ (R\text{-}R + 0.07)]}$, and the upper limit of normal as stated by him was 0.410 for men and 0.420 for women. These are summarized in Table I.

TABLE I. SUMMARY OF FORMULAS USED IN THIS WORK AND THEIR UPPER LIMIT AT NORMAL

AUTHOR	FORMULA	DERIVATION OF K	UPPER LIMIT OF NORMAL
Bazett[5]	$Q\text{-}T = K\sqrt{R\text{-}R}$	$K = \dfrac{Q\text{-}T}{\sqrt{R\text{-}R}}$	American Heart Association[14] 0.392 (male) 0.440 (female) Shipley and Hallaran[18] 0.443 (male) 0.456 (female)
Fridericia[10]	$Q\text{-}T = K\sqrt[3]{R\text{-}R}$	$K = \dfrac{Q\text{-}T}{\sqrt[3]{R\text{-}R}}$	8.22*
Ashman[3]	$Q\text{-}T = K \log [10\ (R\text{-}R + 0.07)]$	$K = \dfrac{Q\text{-}T}{\log [10\ (R\text{-}R + 0.07)]}$	0.410 (male) 0.429 (female)

*Only normal has been ascertained to date in literature.

TABLE II. DATA ON CASES FROM LOCAL HOSPITALS

AGE	SEX	Q-T	R-R	$\frac{Q\text{-}T}{T\text{-}Q}$	$Q\text{-}T_B$	$Q\text{-}T_A$	$Q\text{-}T_F$
53	M	0.30	0.71	0.723	0.354	0.336	0.726
29	F	0.32	0.44	2.662	0.483	0.453	0.907
25	M	0.41	0.64	1.781	0.641	0.482	1.025
		0.40	0.78	1.052	0.453	0.430	0.936
		0.35	0.86	0.686	0.377	0.362	0.847
60	F	0.32	0.53	1.548	0.440	0.422	0.853
59	M	0.36	0.63	1.362	0.454	0.426	0.906
		0.35	0.59	1.458	0.456	0.427	0.900
74	F	0.38	0.75	1.027	0.438	0.421	0.901
32	F	0.35	0.84	0.718	0.382	0.365	0.789
23	F	0.36	0.75	0.923	0.418	0.395	0.853
62	F	0.37	0.73	1.028	0.434	0.409	0.885
81	M	0.32	0.73	0.781	0.375	0.354	0.765
50	M	0.31	0.63	0.968	0.392	0.389	0.780
62	M	0.39	0.74	1.112	0.453	0.430	0.929
47	M	0.39	0.78	1.000	0.442	0.421	0.912
45	M	0.43	0.66	1.870	0.530	0.498	1.065
		0.41	0.67	1.463	0.502	0.472	1.009
44	F	0.29	0.54	1.160	0.398	0.369	0.769
		0.30	0.54	1.250	0.409	0.382	0.794
51	M	0.46	0.63	2.702	0.581	0.541	1.158
		0.29	0.51	0.906	0.414	0.381	0.782
54	M	0.28	0.61	0.848	0.385	0.337	0.713
35	M	0.36	0.82	0.783	0.397	0.379	0.832
		0.38	0.85	0.808	0.412	0.395	0.865
35	F	0.39	0.65	1.498	0.484	0.454	0.973
		0.35	0.63	1.249	0.442	0.414	0.882
31	F	0.32	0.58	1.231	0.421	0.394	0.823
		0.31	0.53	1.407	0.426	0.398	0.826
66	M	0.32	0.88	0.572	0.342	0.328	0.729
56	F	0.35	0.55	1.747	0.472	0.432	0.920
44	M	0.36	0.62	1.385	0.458	0.430	0.912
29	F	0.32	0.60	1.142	0.414	0.387	0.818
21	M	0.41	0.84	0.953	0.447	0.427	0.936
		0.34	0.57	1.479	0.451	0.432	0.884
		0.35	0.59	1.458	0.456	0.438	0.899
		0.28	0.41	2.152	0.437	0.412	0.813
		0.31	0.50	1.632	0.439	0.410	0.841
68	F	0.41	0.67	1.578	0.502	0.472	1.009
53	F	0.25	0.44	1.318	0.378	0.352	0.709
61	F	0.28	0.65	0.751	0.347	0.329	0.698
		0.30	0.64	0.883	0.375	0.352	0.750
		0.26	0.61	0.744	0.333	0.312	0.662
59	F	0.29	0.43	2.070	0.432	0.416	0.827
37	M	0.30	0.56	1.152	0.402	0.378	0.784
52	M	0.32	0.46	2.282	0.472	0.442	0.893
60	M	0.36	0.72	1.000	0.424	0.401	0.864
		0.35	0.70	1.000	0.418	0.399	0.850
62	M	0.40	0.80	1.000	0.446	0.426	0.928
		0.44	0.83	1.128	0.484	0.461	1.008
		0.41	0.79	1.079	0.457	0.439	0.958
53	M	0.32	0.54	1.453	0.437	0.412	0.847
54	M	0.36	0.76	0.900	0.414	0.392	0.853
61	M	0.30	0.42	2.500	0.463	0.434	0.865
53	M	0.27	0.57	0.900	0.358	0.335	0.693
37	M	0.34	0.73	0.872	0.399	0.377	0.814
59	F	0.28	0.48	1.400	0.404	0.379	0.772
37	M	0.30	0.56	1.155	0.401	0.376	0.784
61	M	0.38	0.60	1.750	0.492	0.448	0.971
43	M	0.35	0.85	0.718	0.387	0.364	0.797
		0.34	0.81	0.918	0.378	0.361	0.787

TABLE II.—CONT'D

AGE	SEX	Q-T	R-R	$\frac{\text{Q-T}}{\text{T-Q}}$	Q-T_B	Q-T_A	Q-T_F
61	M	0.44	0.72	1.571	0.519	0.491	1.055
52	M	0.31	0.48	1.823	0.448	0.419	0.855
25	M	0.42	0.71	1.470	0.498	0.480	1.015
		0.42	0.64	1.909	0.525	0.493	1.050
		0.39	0.61	1.772	0.499	0.469	0.994
		0.34	0.66	1.087	0.419	0.395	0.843
		0.34	0.62	1.214	0.432	0.406	0.862
43	M	0.48	0.77	1.655	0.547	0.518	1.125
46	M	0.37	0.53	2.306	0.509	0.476	0.988
30	M	0.35	0.56	1.688	0.468	0.439	0.915
		0.32	0.53	1.522	0.440	0.412	0.854
33	M	0.40	0.67	1.482	0.489	0.461	0.984
		0.38	0.68	1.268	0.461	0.435	0.932
67	M	0.33	0.52	1.785	0.458	0.428	0.886
68	M	0.30	0.46	1.875	0.434	0.415	0.838

TABLE III. DATA ON CASES FROM LITERATURE

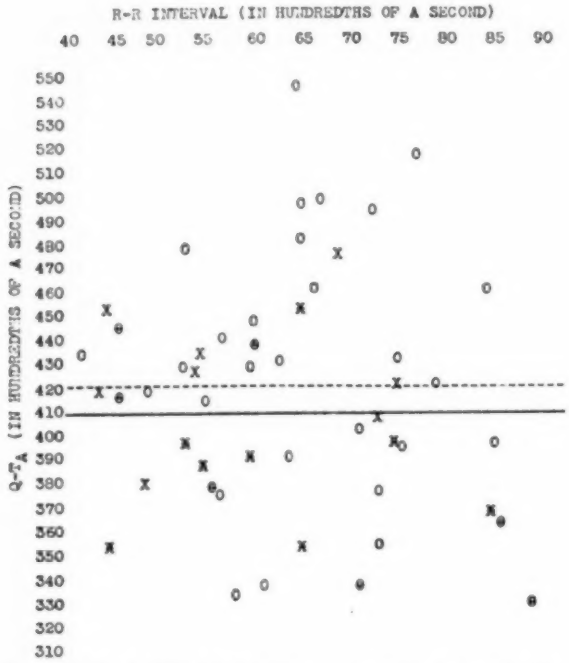
AGE	SEX	Q-T	R-R	$\frac{\text{Q-T}}{\text{T-Q}}$	Q-T_B	Q-T_A	Q-T_F
28	F	0.26	0.41	1.732	0.406	0.382	0.754
25	M	0.63	1.60	0.551	0.476	0.494	1.117
24	M	0.40	1.10	0.530	0.375	0.375	0.836
21	M	0.36	0.61	1.439	0.455	0.433	0.915
36	M	0.29	0.53	1.077	0.393	0.373	0.773
		0.30	0.52	1.448	0.407	0.389	0.804
48	M	0.29	0.54	1.160	0.396	0.369	0.769
67	M	0.36	0.55	1.802	0.492	0.454	0.947
25	M	0.31	0.54	1.345	0.421	0.395	0.821
		0.32	0.48	2.000	0.462	0.432	0.881
20	M	0.49	0.92	1.139	0.511	0.492	1.085
34	M	0.52	0.82	1.731	0.574	0.548	1.202
40	M	0.56	1.00	1.272	0.560	0.545	1.210
58	M	0.27	0.48	1.285	0.380	0.361	0.744
		0.28	0.43	1.865	0.426	0.401	0.799
29	M	0.29	0.49	1.450	0.415	0.390	0.794
		0.40	0.58	2.210	0.526	0.492	1.032
31	F	0.22	0.28	3.770	0.416	0.406	0.732
55	F	0.50	0.67	3.105	0.611	0.619	1.230
		0.28	0.48	1.400	0.410	0.379	0.771
		0.40	0.60	2.000	0.518	0.445	1.021
52	M	0.34	0.56	1.700	0.474	0.426	0.888
		0.40	0.90	0.800	0.423	0.406	0.894
		0.35	0.64	1.208	0.437	0.412	0.875
44	M	0.52	0.74	2.362	0.604	0.572	1.239
44	M	0.50	1.02	0.735	0.449	0.483	1.071
78	F	0.52	0.95	1.209	0.534	0.516	1.138
68	F	0.54	1.12	0.931	0.511	0.502	1.120
52	F	0.52	0.80	1.855	0.582	0.554	1.205
40	M	0.64	1.20	1.142	0.585	0.579	1.300
69	M	0.50	1.12	0.817	0.484	0.467	1.038
35	F	0.46	0.90	1.045	0.486	0.467	1.028
57	M	0.92	1.48	1.641	0.757	0.672	1.742
69	M	0.40	0.88	0.835	0.427	0.409	0.902
56	F	0.42	0.70	1.500	0.503	0.474	1.018
51	M	0.48	0.84	1.332	0.523	0.501	1.096

RESULTS

Table II shows the findings in the cases from the local hospitals and Table III the findings collected from the literature. Tables IV and V summarize the distribution.

TABLE IV. DISTRIBUTION OF CASES FROM LOCAL HOSPITALS

(Details on Table II)



Broken line denotes upper limit of normal for women. Continuous line denotes upper limit of normal for men.

o = male patient, nonrheumatic; x = female patient, nonrheumatic; o with a line through it = male patient, rheumatic; x with a line through it = female patient, rheumatic.

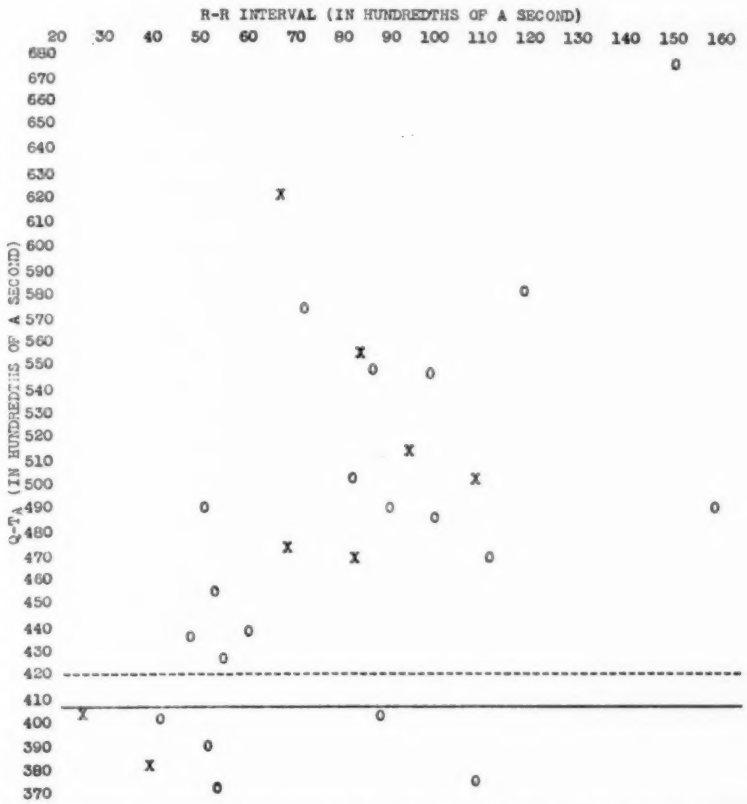
In the fifty-one autopsied cases from the local hospitals, $Q\text{-}T_B$ was higher than the American Heart Association upper limit of normal in thirty-two cases (62.7 per cent) and above Shipley and Hallaran's range in twenty-six cases (51.0 per cent). $Q\text{-}T_F$ was above the normal in thirty-five (68.7 per cent). $Q\text{-}T_A$ was above the upper limit of normal in twenty-eight (54.9 per cent). $\frac{Q\text{-}T}{T\text{-}Q}$ was 1.0 or greater in thirty-eight cases (74.5 per cent).

In the above series, there were sixteen cases with serial electrocardiograms. Five (31.2 per cent) showed a direct relationship between an increase in the $\frac{Q\text{-}T}{T\text{-}Q}$ ratio and the progression of the severity of the disease. Four of these five (20 per cent of total) showed a direct relationship between an increase in the constants and the course of the disease.

In the twenty-eight autopsied cases collected from the literature, $Q\text{-}T_B$ was above the American Heart Association upper limit of normal in twenty-five (89.3 per cent) and above Shipley and Hallaran's range in twenty-one (75.0 per cent). $Q\text{-}T_P$ was above the normal in twenty-three cases (82.2 per cent). $Q\text{-}T_A$ was above the upper limit of normal in twenty-one (75.0 per cent). $\frac{Q\text{-}T}{T\text{-}Q}$ was 1.0 or greater in twenty-two out of twenty-eight cases (78.6 per cent).

TABLE V. DISTRIBUTION OF CASES FROM THE LITERATURE

(Details on Table III)



Broken line denotes upper limit of normal for women. Continuous line denotes upper limit of normal for men.

o = male patient; x = female patient. All patients are nonrheumatic.

In the cases collected from the literature, there were six cases with serial electrocardiograms. Of these, four (67.0 per cent) showed a direct relationship between both the $\frac{Q\text{-}T}{T\text{-}Q}$ ratio and the constants and the course of the disease.

In those cases presenting serial electrocardiograms, all which had at least one tracing showing a prolonged Q-T interval were listed as above the upper limit of normal.

These findings are summarized in Table VI.

TABLE VI. COMPARISON OF CONSTANTS IN CASES FROM LOCAL HOSPITALS AND CASES FROM THE LITERATURE

FORMULA USED	DATA FROM LOCAL HOSPITALS (%)	DATA FROM LITERATURE (%)
$Q\text{-}T_B$ (AHA)*	67.2	89.3
(S and H)†	51.0	75.0
$Q\text{-}T_A$	54.9	75.0
Taran's series ($Q\text{-}T_A$)	62.0	
$Q\text{-}T_F$	68.7	82.2
$\frac{Q\text{-}T}{T\text{-}Q}$	74.5	78.6

*AHA = American Heart Association standard.[14]
†S and H = Shipley and Hallaran's range.[18]

In the cases collected from the local hospitals, there were fourteen rheumatic and thirty-seven nonrheumatic. Of the fourteen rheumatic, $Q\text{-}T_B$ was above the upper limit of normal in four (28.6 per cent), using the American Heart Association data, and in three (21.4 per cent), using Shipley and Hallaran's range. $Q\text{-}T_A$ was above the upper limit in three cases (21.4 per cent) and $Q\text{-}T_F$ in five (35.7 per cent). $\frac{Q\text{-}T}{T\text{-}Q}$ was above normal in seven cases (50.0 per cent). In contrast, in the thirty-seven nonrheumatic cases, $Q\text{-}T_B$ was above the American Heart Association limit in twenty-eight cases (75.8 per cent) and above Shipley and Hallaran's range in twenty-three (62.2 per cent). $Q\text{-}T_A$ was above the normal limit in twenty-five cases (67.6 per cent) and $Q\text{-}T_F$ above the normal in thirty (81.0 per cent). $\frac{Q\text{-}T}{T\text{-}Q}$ was above normal in twenty-four cases (64.9 per cent). This is summarized in Table VII.

TABLE VII. COMPARISON OF CONSTANTS IN RHEUMATIC CASES AND NONRHEUMATIC CASES

FORMULA USED	RHEUMATIC (%)	NONRHEUMATIC (%)
$Q\text{-}T_B$ (AHA)*	28.6	75.8
(S and H)†	21.4	62.2
$Q\text{-}T_A$	21.4	67.6
$Q\text{-}T_F$	35.7	81.0
$\frac{Q\text{-}T}{T\text{-}Q}$	50.0	64.9

*AHA = American Heart Association standard.[14]
†S and H = Shipley and Hallaran's range.[18]

Since the calculation of the $\frac{Q\text{-}T}{T\text{-}Q}$ ratio is much simpler and quicker than the calculation of any of the constants, the cases were studied to determine the correlation between $\frac{Q\text{-}T}{T\text{-}Q}$ and $Q\text{-}T_A$. In the seventy-six electrocardiograms taken of the

fifty-one cases from the local hospitals, there was agreement of both $\frac{Q\text{-}T}{T\text{-}Q}$ and $Q\text{-}T_A$ (either above normal or below normal) in fifty-eight (76.4 per cent); in the thirty-six electrocardiograms taken of the twenty-eight cases collected from the literature there was correlation between $\frac{Q\text{-}T}{T\text{-}Q}$ and $Q\text{-}T_A$ in twenty-two (61.1 per cent). $\frac{Q\text{-}T}{T\text{-}Q}$ was above normal, while $Q\text{-}T_A$ was normal in twenty-seven (81.5 per cent) of the thirty-two electrocardiograms in which $\frac{Q\text{-}T}{T\text{-}Q}$ and $Q\text{-}T_A$ were not in agreement. In the remaining five cases the reverse occurred (18.5 per cent). See Tables VIII and IX.

TABLE VIII. COMPARISON OF THE CASES IN WHICH $\frac{Q\text{-}T}{T\text{-}Q}$ AND $Q\text{-}T_A$ WERE IN AGREEMENT

LOCAL HOSPITALS	LITERATURE
76.4%	61.1%

TABLE IX. RELATION OF $\frac{Q\text{-}T}{T\text{-}Q}$ AND $Q\text{-}T_A$ IN CASES IN WHICH THERE WAS NO AGREEMENT

$\frac{Q\text{-}T}{T\text{-}Q}$ ABOVE NORMAL $Q\text{-}T_A$ NORMAL	$\frac{Q\text{-}T}{T\text{-}Q}$ NORMAL $Q\text{-}T_A$ ABOVE NORMAL
18.5%	81.5%

COMMENT

Taran[23] stated: "The upper limit of the normal $Q\text{-}T_c$* for children is 0.405 second† . . . all with acute carditis have a systole significantly longer than the upper limit of normal." Examination of Taran's reference 4 will show the formula used for the above-mentioned normal is Ashman's not Bazett's, and that Ashman's upper limit of normal was applied to Bazett's formula, which results in a considerable difference.‡ In this series of fifty-one cases from the local hospitals, $Q\text{-}T_B$ was found to be always at least 0.020 second higher than $Q\text{-}T_A$.

Since there is no upper limit of normal set down by the American Heart Association for Bazett's formula, all of Taran's cases were recalculated using Ashman's formula and then the figures were applied to Ashman's upper limit of normal (Table X). Nineteen of the fifty cases were found to be 0.405 second or under, leaving thirty-seven cases (62.0 per cent) above the upper limit of normal. This corrected percentage is very similar to that found in our series of adults who died from all types of acute myocarditis. This is compared with our findings in Table VI.

*$Q\text{-}T_c$ = $Q\text{-}T_B$ in this paper.

†At this point there is a reference to 4.

‡Dr. Taran stated in a personal communication to the authors that, despite this discrepancy, the Q-T interval, corrected according to Bazett's formula, was 0.405 in his series of normal children.

TABLE X. RECALCULATION OF THE CASES OF TARAN IN WHICH THE CONSTANT FELL BELOW NORMAL

R-R	Q-T	$Q\text{-}T_B$	$\frac{Q\text{-}T}{T\text{-}Q}$	$Q\text{-}T_A$
70	0.3580	0.423	1.05	0.404
68	0.3520	0.428	1.08	0.402
62	0.3340	0.425	1.15	0.399
61	0.3292	0.423	1.14	0.395
59	0.3280	0.426	1.17	0.405
57	0.3200	0.421	1.22	0.397
56	0.3192	0.428	1.34	0.399
54	0.3150	0.428	1.36	0.401
53	0.3144	0.432	1.31	0.404
52	0.3028	0.420	1.38	0.389
50	0.2984	0.419	1.45	0.398
50	0.2920	0.413	1.35	0.386
49	0.2920	0.415	1.45	0.391
49	0.2920	0.418	1.49	0.391
48	0.2960	0.427	1.64	0.399
47	0.2912	0.425	1.63	0.398
46	0.2924	0.429	1.62	0.404
44	0.2864	0.430	1.55	0.405
39	0.2628	0.430	2.04	0.397

DISCUSSION

The diagnosis of acute myocarditis has been considered a difficult one for many years. Only in recent years has it been emphasized that many patients die of acute myocarditis which is not of rheumatic or diphtheritic etiology. It was believed that if a valuable diagnostic and prognostic criterion could be found, it would aid in the diagnosis and management of this little-considered disease entity. Of 237 patients with autopsy-diagnosed acute myocarditis at one hospital, 49 had electrocardiograms. Therefore, in only 20.7 per cent of the patients was cardiac involvement considered by the attending physicians. There is a very small error in this figure because a few patients died too soon after entry to have electrocardiograms taken. It is impossible to break down these cases into rheumatic and nonrheumatic, but, since the predominant number of rheumatic carditis patients had electrocardiograms taken, the percentage of nonrheumatic myocarditis deaths in which cardiac involvement was considered (as reflected by the presence of an electrocardiogram) was even smaller than 20 per cent.

On the other hand, Table VII shows that the Q-T interval was prolonged two to three times more often in nonrheumatic myocarditis than rheumatic myocarditis. Therefore, fortunately, more consistent aid would be expected from the Q-T interval prolongation in the difficult diagnosis of this entity than in rheumatic myocarditis, which has a more clearly defined clinical picture. It is very possible that the higher percentage of abnormal Q-T intervals found in the cases collected from the literature is due to the fact that all were of nonrheumatic etiology in that group.

Using the various formulas for the corrected Q-T, it was found in proved autopsy cases that in a moderate percentage (20 to 67.0 per cent), the progress of the disease could be followed by the change in the constants. A still higher percentage (51.0 to 74.5 per cent) of this series showed prolonged constants as an

index of the presence of acute myocarditis, and, therefore, the prolongation would be of aid in making the diagnosis.

It should be emphasized that while prolongation of the constants is of significance in making the diagnosis of acute myocarditis, a normal Q-T interval does not rule out such a diagnosis.

Since the correlation between Q-T_A and $\frac{Q\text{-}T}{T\text{-}Q}$ ratio was found in 61.1 and 76.4 per cent of the electrocardiograms in the two series, the $\frac{Q\text{-}T}{T\text{-}Q}$ ratio was again shown to be a simple means of determining prolongation of the Q-T interval. However, since, in the electrocardiograms which did not show agreement between $\frac{Q\text{-}T}{T\text{-}Q}$ and Q-T_A, the predominant number showed $\frac{Q\text{-}T}{T\text{-}Q}$ to be above normal while Q-T_A was not, it is apparent that Q-T_A is a more conservative and accurate criterion—a normal $\frac{Q\text{-}T}{T\text{-}Q}$ being very significant, while one above normal would warrant calculation of one of the constants.

Correlation of many studies of the normal Q-T interval with our findings indicates that more nearly correct results are achieved by using Ashman's formula than any other. Especially important is the fact that if Bazett's formula is to be used, as by the American Heart Association's "Nomenclature and Criteria for Diagnosis," the upper limit of normal should be considerably higher than that quoted there.

Most important is the therapeutic implication of this study. It is admitted that therapeutically there is little that can be offered a patient with acute myocarditis (with the possible exception of the newer antibiotics), even after the diagnosis is made with some degree of certainty. It may very well be that more judicious use of prolonged bed rest, as is used in rheumatic fever, would prevent many of the deaths due to acute myocarditis following the acute infectious diseases. It is here that the use of the Q-T interval as a diagnostic measure, and especially as a measure of when to let the patient out of bed, becomes important.

SUMMARY

1. The electrocardiograms of fifty-one cases of autopsy-proved acute myocarditis were studied to ascertain the corrected Q-T intervals.

2. Depending on the formula used, Q-T was prolonged above the upper limit of normal in 51.0 to 89.3 per cent of the cases.

3. Dividing our series into rheumatic and nonrheumatic, Q-T was prolonged in 21.4 to 35.7 per cent of the former group (depending on the formula used) and 62.2 to 81.0 per cent of the latter group.

4. $\frac{Q\text{-}T}{T\text{-}Q}$ and Q-T_A were in agreement in 61.1 to 76.4 per cent of the cases. Q-T_A was shown to be a more conservative and accurate criterion, however.

5. Attention is directed to the consideration of acute myocarditis as part of the pathologic manifestations of acute infectious processes.

6. The prolongation of the corrected Q-T interval is offered as an aid in the diagnosis of acute myocarditis.

7. Emphasis is made on bed rest as the important therapeutic measure whenever acute myocarditis is diagnosed or suggested. The return of the corrected Q-T to normal is suggested as an index of when to let the patient out of bed.

8. Q-T was more consistently prolonged in acute nonrheumatic myocarditis than in acute rheumatic myocarditis.

9. The physiologic background for expecting a prolonged systole in acute myocarditis and the various formulas which have been proposed for correcting the Q-T interval for rate have been reviewed.

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UNIPOLAR ELECTROCARDIOGRAM IN NORMAL INFANTS AND CHILDREN

PAUL N. G. YU, M.D., HOWARD A. JOOS, M.D., AND CHRIS P. KATSAMPES, M.D.

ROCHESTER, N. Y.

PRIOR to 1947, the electrocardiographic studies on infants and children were confined mainly to the three standard and one or more precordial leads.[1-5] Since use of three unipolar limb and six unipolar precordial leads has become more widespread, only a few reports on this type of electrocardiogram in infants and children have appeared in the recent literature.[6-8] Because the number of normal infants and children studied is still small, further studies in a comparatively large series of children are indicated. This report was planned to serve as a control for future studies of unipolar electrocardiography in infants and children in this hospital. Inasmuch as data on the three standard limb leads have been widely reported by many workers, no attempt was made to include studies of these leads in this report. Only data on the three augmented unipolar limb and six unipolar precordial leads are presented with the exception of the measurement of the Q-T interval for which the three standard limb leads were also included.

MATERIAL AND METHOD

One hundred infants and children between the ages of 8 days and 14 years were selected for this study. They were arbitrarily divided into the following five age groups (Table I):

Group I	0 to 2 years
Group II	2 to 4 years
Group III	5 to 7 years
Group IV	8 to 10 years
Group V	11 to 14 years

Subjects were picked at random from the Pediatric Service and Diagnostic Clinic of the hospital. None of them had a history, physical signs, laboratory or roentgenologic evidence of rheumatic fever or cardiovascular disease.

Routine electrocardiograms included three standard limb leads, three augmented unipolar limb leads (aV_L, aV_R, and aV_F) according to the technique of Goldberger, and unipolar precordial leads (V_1, V_2, V_3, V_4, V_5, and V_6) taken from the six points recommended by the American Heart Association. All the tracings were recorded in the recumbent position with the children at rest. In most of the cases two or more tracings were taken on each subject. The Edin direct writing machine was used throughout this study.

From the Departments of Medicine and Pediatrics of the University of Rochester School of Medicine and Dentistry, and the Strong Memorial and Rochester Municipal Hospitals, Rochester.

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TABLE I. AGE AND SEX

GROUP	AGE (YEARS)	SEX		TOTAL
		BOYS	GIRLS	
I	0 to 2	9	7	16
II	2 to 4	8	8	16
III	5 to 7	23	14	37
IV	8 to 10	6	10	16
V	11 to 14	10	5	15
Grand total		56	44	100

The electrical positions of the heart were classified as vertical, semivertical, intermediate, semihorizontal, and horizontal, as suggested by Wilson and associates.[9] The measurements of the various components of the electrical cycle were made in all the unipolar limb and precordial leads in the usual manner. Amplitudes of the complexes were measured in millimeters and the time intervals in seconds. All the values have been treated statistically. The Q-T interval and the cycle length were measured, with the aid of a hand magnifying lens, in the shortest and longest cycle of each of the three standard limb and three unipolar precordial leads (usually V_2, V_4, and V_5). The average value of these twelve measurements was taken for the computation of the corrected Q-T interval according to the modified formula of Bazett.[10] $Q\text{-}T_c = \frac{Q\text{-}T}{\sqrt{RR}}$, where Q-T is the Q-T interval in seconds, and RR is the cycle length in seconds.

RESULTS

Heart Rate.—The heart rate is given in Table II. The rate in infants under 2 years of age varied between 107 and 156 per minute with an average value of 127. In all the other four groups of children, the average heart rate was below 100 per minute although the range was quite wide. In general, the younger the children, the faster the heart rate.

TABLE II. HEART RATE

HEART RATE PER MINUTE	GROUP I (2 YEARS OR LESS)	GROUP II (2 TO 4 YEARS)	GROUP III (5 TO 7 YEARS)	GROUP IV (8 TO 10 YEARS)	GROUP V (11 TO 14 YEARS)
60 or less	0	0	0	0	1
61 to 100	0	7	30	15	12
101 to 120	5	8	7	0	1
121 to 140	9	1	0	0	1
141 or greater	2	0	0	1	0
Average	127.0	99.2	88.4	81.2	81.0
Range	107–156	72–125	71–109	62–142	55–126

Electrical Position of the Heart.—The electrical position of the heart in different age groups is given in Table III. Most of the infants and children had vertical or semivertical positions. Semihorizontal position was present in only

three children. None of the children had a horizontal position of the heart. These findings confirmed the results obtained by Switzer and Besoain[7] on a group of fifty-two normal children, i.e., semihorizontal and horizontal positions were unusual.

TABLE III. ELECTRICAL POSITION OF THE HEART

AGE GROUP (YEARS)	TOTAL NO. CASES	VERTICAL		SEMI-VERTICAL		INTER-MEDIATE		SEMIHORI-ZONTAL		HORIZONTAL	
		NO. CASES	%	NO. CASES	%	NO. CASES	%	NO. CASES	%	NO. CASES	%
I (2 or less)	16	8	50	3	19	5	31	0	0	0	0
II (2 to 4)	16	9	56	5	31	2	13	0	0	0	0
III (5 to 7)	37	17	46	13	35	5	14	2	5	0	0
IV (8 to 10)	16	11	69	3	19	1	7	1	7	0	0
V (11 to 14)	14	6	43	5	38	3	21	0	0	0	0
Grand total	99	51		29		16		3		0	

Auricular Complex.—Table IV shows the voltage of the P wave in the various leads. The P wave was invariably negative in aV_R, always positive in aV_F, and variable in aV_L. In some instances the P wave was negative in V_1, especially in children under 5 years of age. From V_2 to V_6 the P wave was either isoelectric or positive. In the unipolar limb leads the voltage of the P wave was highest in aV_R and aV_F, whereas in the precordial leads its highest voltage was noted in V_2, V_3, and V_4.

Duration of P-R Interval.—Data showing the duration of the P-R interval are presented in Table V. The over-all duration of the P-R interval in the unipolar limb and precordial leads was not significantly different from that obtained in the standard limb leads by other authors. The P-R interval was usually shorter in aV_L than in the two remaining unipolar limb leads. This is in accord with the observations of Switzer and Besoain.[7] In the precordial leads there was no significant difference in the duration of the P-R interval. The average duration of the P-R interval was directly proportional to the age of the subject, and inversely proportional to the heart rate.

Duration of QRS Complex.—Table VI shows that in children the average duration of the QRS complex is shorter than that reported in adults. It is of interest to note that the average duration of the QRS complex did not vary significantly in any of the five age groups. The measurements ranged from 0.04 second to 0.08 second. The duration was frequently shortest in aV_L and aV_R, longest in V_2, V_3, and V_4, and intermediate in the remainder of the unipolar limb and precordial leads.

TABLE IV. HEIGHT OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	0.8	−0.1	0.1	±0.23	16	1.0	−0.5	0.2	±0.33	37	2.0
aV_R	16	−0.1	−1.5	−0.8	±0.35	16	−0.5	−1.2	−0.9	±0.26	37	−0.2
aV_F	16	1.5	0.2	0.8	±0.34	16	1.5	0.0	0.6	±0.45	37	2.0
V_1	16	1.2	−0.5	0.1	±0.47	16	1.0	−0.2	0.5	±0.42	35	1.2
V_2	16	1.5	0.0	0.4	±0.39	16	1.0	0.1	0.4	±0.28	37	1.8
V_3	16	1.0	0.0	0.4	±0.30	16	1.0	0.1	0.3	±0.29	35	1.0
V_4	16	1.0	0.1	0.3	±0.27	16	1.0	0.1	0.4	±0.23	37	1.0
V_5	16	1.0	0.1	0.4	±0.29	16	0.5	0.0	0.3	±0.17	37	1.0
V_6	16	1.5	0.1	0.5	±0.34	16	1.0	0.0	0.3	±0.25	35	1.0

TABLE V. DURATION OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	9	0.12	0.07	0.11	±0.020	15	0.15	0.09	0.12	±0.016	32	0.15
aV_R	16	0.14	0.09	0.12	±0.015	16	0.15	0.09	0.13	±0.013	37	0.15
aV_F	16	0.14	0.10	0.12	±0.012	15	0.15	0.10	0.13	±0.013	35	0.16
V_1	14	0.14	0.09	0.12	±0.018	16	0.15	0.10	0.13	±0.012	32	0.15
V_2	16	0.14	0.10	0.12	±0.012	16	0.15	0.10	0.13	±0.013	36	0.15
V_3	15	0.14	0.10	0.12	±0.013	16	0.14	0.11	0.13	±0.009	33	0.15
V_4	16	0.14	0.09	0.12	±0.016	16	0.15	0.11	0.13	±0.010	37	0.15
V_5	16	0.14	0.09	0.12	±0.015	15	0.16	0.10	0.13	±0.014	34	0.15
V_6	16	0.14	0.09	0.12	±0.015	14	0.14	0.11	0.13	±0.010	30	0.15

TABLE VI. DURATION OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	0.06	0.04	0.05	±0.008	16	0.06	0.04	0.05	±0.007	35	0.07
aV_R	16	0.06	0.04	0.06	±0.014	16	0.07	0.04	0.05	±0.009	35	0.08
aV_F	16	0.06	0.04	0.05	±0.009	16	0.07	0.04	0.06	±0.011	35	0.08
V_1	16	0.08	0.04	0.06	±0.009	16	0.08	0.05	0.07	±0.009	33	0.08
V_2	16	0.08	0.05	0.06	±0.011	16	0.08	0.05	0.07	±0.008	35	0.08
V_3	16	0.08	0.05	0.06	±0.009	16	0.07	0.06	0.07	±0.002	33	0.08
V_4	16	0.08	0.05	0.06	±0.013	16	0.08	0.05	0.06	±0.009	35	0.08
V_5	16	0.07	0.04	0.06	±0.008	16	0.07	0.05	0.06	±0.007	35	0.08
V_6	16	0.07	0.04	0.05	±0.009	15	0.07	0.05	0.06	±0.010	32	0.07

P Wave in Millimeters

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
−0.5	0.3	±0.41	16	0.6	−0.2	0.2	±0.21	15	0.6	−0.1	0.2	±0.18
−1.5	−0.8	±0.31	16	−0.5	−1.0	−0.8	±0.22	15	−0.3	−1.5	−0.8	±0.33
0.1	0.5	±0.41	16	1.5	0.2	0.7	±0.38	15	1.5	0.0	0.5	±0.46
0.1	0.4	±0.41	15	1.5	−0.2	0.5	±0.41	14	1.0	0.0	0.3	±0.81
0.2	0.4	±0.37	16	1.0	0.0	0.4	±0.34	15	1.5	0.0	0.4	±0.38
0.1	0.4	±0.29	15	1.0	0.2	0.4	±0.27	14	1.2	0.1	0.4	±0.29
0.1	0.3	±0.28	16	0.8	0.1	0.3	±0.63	15	0.5	0.1	0.3	±0.16
0.0	0.3	±0.25	16	0.5	0.1	0.3	±0.15	15	0.5	0.1	0.2	±0.17
0.0	0.3	±0.25	15	1.0	0.0	0.3	±0.26	14	0.5	0.1	0.3	±0.17

P-R Interval in Seconds

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0.10	0.12	±0.014	14	0.18	0.10	0.13	±0.020	13	0.17	0.10	0.13	±0.017
0.10	0.13	±0.010	16	0.17	0.12	0.14	±0.013	15	0.15	0.12	0.14	±0.010
0.12	0.14	±0.012	16	0.18	0.12	0.14	±0.012	13	0.15	0.12	0.14	±0.008
0.11	0.13	±0.011	15	0.18	0.11	0.13	±0.016	13	0.15	0.13	0.14	±0.008
0.10	0.13	±0.012	16	0.17	0.12	0.13	±0.015	15	0.15	0.13	0.14	±0.007
0.11	0.13	±0.011	15	0.17	0.12	0.14	±0.014	14	0.15	0.12	0.13	±0.009
0.10	0.13	±0.033	16	0.17	0.12	0.14	±0.015	15	0.16	0.12	0.14	±0.012
0.11	0.13	±0.032	16	0.17	0.12	0.14	±0.015	15	0.15	0.12	0.14	±0.008
0.11	0.13	±0.010	14	0.18	0.12	0.13	±0.019	14	0.14	0.12	0.13	±0.007

QRS Interval in Seconds

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0.04	0.05	±0.009	16	0.06	0.04	0.05	±0.007	14	0.07	0.04	0.05	±0.011
0.04	0.05	±0.009	16	0.06	0.05	0.05	±0.005	14	0.08	0.04	0.05	±0.009
0.04	0.05	±0.009	16	0.06	0.05	0.06	±0.007	14	0.08	0.05	0.06	±0.009
0.05	0.07	±0.008	15	0.08	0.05	0.07	±0.008	13	0.08	0.06	0.07	±0.007
0.06	0.07	±0.006	16	0.08	0.05	0.07	±0.009	14	0.08	0.06	0.07	±0.006
0.05	0.07	±0.008	15	0.08	0.05	0.07	±0.008	13	0.08	0.06	0.07	±0.006
0.05	0.07	±0.008	16	0.08	0.05	0.07	±0.009	14	0.08	0.06	0.06	±0.005
0.05	0.06	±0.008	16	0.08	0.05	0.07	±0.008	14	0.08	0.05	0.06	±0.007
0.05	0.06	±0.005	15	0.07	0.05	0.06	±0.007	13	0.08	0.05	0.06	±0.008

TABLE VII. DEPTH OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	0.5	0	0.03	±0.13	16	1.0	0	0.16	±0.30	37	1.0
aV_R	16	10.5	0	1.6	±0.34	16	10.0	0	2.9	±3.7	37	10.0
aV_F	16	4.0	0	1.2	±1.29	16	4.0	0	1.26	±1.3	37	3.0
V_1	16	0	0	0	0	16	0	0	0	0	37	0
V_2	16	0	0	0	0	16	0	0	0	0	37	0
V_3	16	0	0	0	0	16	0	0	0	0	35	0.5
V_4	16	3.0	0	0.25	±0.75	16	1.5	0	0.19	±0.40	37	2.5
V_5	16	3.0	0	0.6	±0.92	16	3.0	0	1.2	±0.91	37	5.0
V_6	16	3.0	0	0.9	±0.10	16	5.0	0	1.9	±1.4	35	3.0

TABLE VIII. HEIGHT OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	8.0	0.5	4.0	±2.6	16	7.0	0.5	3.1	±1.8	37	9.0
aV_R	16	4.0	0.5	1.1	±1.1	16	3.0	0	1.3	±1.0	37	6.5
aV_F	16	16.0	0.5	8.8	±4.8	16	19.5	0.5	9.5	±5.0	37	19.8
V_1	16	14.5	1.0	7.0	±3.7	16	14.0	2.0	7.5	±3.5	35	16.0
V_2	16	22.0	4.5	13.0	±5.7	16	25.0	5.0	12.7	±5.7	37	20.0
V_3	16	24.0	3.0	14.0	±6.7	16	25.0	6.0	13.4	±5.9	35	42.0
V_4	16	35.0	3.5	20.0	±8.3	16	30.0	9.0	18.5	±6.4	37	37.0
V_5	16	25.0	2.5	16.5	±7.0	16	26.0	10.0	18.4	±5.7	37	35.0
V_6	16	20.0	2.0	12.0	±5.4	16	23.0	8.0	14.6	±4.6	35	20.0

TABLE IX. DEPTH OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	7.0	0	3.4	±2.3	16	6.0	0	2.7	±1.8	37	10.0
aV_R	16	14.0	0	6.3	±4.5	16	14.0	0	5.9	±5.0	37	19.5
aV_F	16	2.5	0	0.72	±0.9	16	14.0	0	2.1	±5.2	37	3.0
V_1	16	14.0	0.5	4.8	±4.5	16	16.0	3.0	8.6	±4.2	35	25.0
V_2	16	21.0	0.5	9.3	±7.1	16	30.0	8.5	16.0	±6.3	37	33.0
V_3	16	23.0	0.5	10.2	±7.0	16	21.0	3.5	12.7	±4.3	35	25.0
V_4	16	22.0	2.0	10.2	±4.9	16	20.0	0	9.0	±4.7	37	26.0
V_5	16	13.0	1.0	6.1	±4.0	16	11.0	0	4.4	±3.7	37	15.0
V_6	16	7.5	0	2.5	±2.4	16	5.0	0.5	1.6	±1.6	35	13.0

Q Wave in Millimeters

GROUP III (5 to 7 years)			GROUP IV (8 to 10 years)					GROUP V (11 to 14 years)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0	0.14	±0.29	16	0.5	0	0.031	±0.30	15	0.5	0	0.03	±0.33
0	1.37	±0.27	16	5.0	0	1.38	±2.16	15	8.0	0	1.0	±0.26
0	0.81	±0.80	16	1.0	0	0.19	±0.20	15	2.0	0	0.43	±0.56
0	0	0	15	0	0	0	0	15	1.5	0	0.11	±0.40
0	0	0	16	0	0	0	0	15	0	0	0	0
0	0.01	±0.12	15	0	0	0	0	14	0	0	0	0
0	0.46	±0.74	16	0	0	0	0	15	1.0	0	0.16	±0.28
0	1.03	±1.0	16	2.5	0	0.31	±0.70	15	2.0	0	0.47	±0.67
0	0.91	±0.48	16	2.0	0	0.57	±0.63	14	2.0	0	0.72	±0.54

R Wave in Millimeters

GROUP III (5 to 7 years)			GROUP IV (8 to 10 years)					GROUP V (11 to 14 years)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0.5	1.9	±1.6	16	8.8	0.5	1.2	±2.2	15	6.0	0.5	1.6	±2.1
0	1.1	±1.2	16	6.0	0.5	1.2	±1.5	15	8.0	0.5	1.2	±2.0
5.0	10.8	±3.4	16	14.0	3.5	8.5	±1.5	15	21.0	5.0	10.5	±4.4
2.5	6.8	±3.2	15	9.0	1.0	3.6	±2.3	14	15.5	0.5	5.1	±5.0
4.5	11.8	±3.7	16	14.5	2.0	7.8	±3.5	15	23.5	1.5	8.3	±5.5
5.5	14.1	±6.5	15	12.5	5.0	8.4	±3.2	14	22.0	3.0	9.2	±5.2
6.0	19.2	±7.1	16	30.0	4.0	14.9	±7.8	15	28.0	7.0	17.2	±6.8
8.0	18.7	±5.5	16	28.0	6.0	17.4	±7.1	15	29.0	6.0	16.4	±6.9
6.0	11.5	±3.4	15	19.1	5.0	12.5	±6.8	14	25.0	4.0	13.5	±5.1

S Wave in Millimeters

GROUP III (5 to 7 years)			GROUP IV (8 to 10 years)					GROUP V (11 to 14 years)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0	3.8	±2.9	16	7.0	0	3.2	±2.0	15	9.0	0	3.1	±2.9
0	7.0	±4.3	16	10.0	0	4.9	±3.7	15	17.0	0	8.3	±4.6
0	0.8	±0.8	16	2.0	0	0.7	±0.6	15	2.5	0	0.8	±1.0
2.0	10.9	±6.1	15	16.0	3.0	8.6	±4.2	14	20.0	0	11.6	±5.0
6.5	11.9	±4.8	16	30.0	8.0	16.8	±6.1	15	36.0	7.0	20.8	±2.4
6.0	11.5	±6.6	15	27.0	8.0	16.3	±4.7	14	30.0	1.0	14.8	±2.4
3.0	9.9	±4.8	16	17.0	4.0	11.2	±4.3	15	16.0	1.0	8.0	±4.4
0.5	4.1	±3.1	16	12.0	0.5	5.7	±3.9	15	8.0	0.5	3.7	±2.4
0	1.4	±7.0	15	4.0	0	1.1	±3.3	14	2.0	0	0.9	±0.8

TABLE X. DURATION OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	9	0.14	0.10	0.12	±0.017	14	0.20	0.10	0.13	±0.026	32	0.19
aV_R	13	0.13	0.10	0.11	±0.011	15	0.15	0.09	0.12	±0.017	37	0.16
aV_F	14	0.14	0.08	0.11	±0.018	16	0.20	0.09	0.13	±0.024	35	0.16
V_1	11	0.14	0.10	0.11	±0.013	16	0.16	0.09	0.12	±0.018	32	0.17
V_2	10	0.14	0.10	0.11	±0.014	15	0.15	0.09	0.12	±0.016	27	0.16
V_3	8	0.12	0.09	0.10	±0.010	10	0.15	0.10	0.12	±0.015	22	0.17
V_4	8	0.13	0.08	0.11	±0.020	13	0.14	0.09	0.11	±0.015	25	0.17
V_5	8	0.12	0.08	0.10	±0.012	15	0.14	0.08	0.11	±0.021	32	0.16
V_6	14	0.12	0.08	0.10	±0.015	15	0.15	0.08	0.12	±0.021	35	0.16

Depth of the Q wave.—As shown in Table VII, the Q wave in the unipolar limb and precordial leads in infants and children has a characteristic distribution. In the unipolar limb leads the Q (or QS) wave was deepest in aV_R, less prominent in aV_F, and only occasionally present in aV_L.

In the precordial leads it was uncommon to find a Q wave in V_1, V_2, and V_3, whereas Q waves were frequently inscribed, in order of increasing depth, in V_4, V_5, and V_6.

The Q wave was more prominent in younger than in older children. The maximum depth of the Q (QS) wave in aV_R was 10.5 mm. and that in V_5 and V_6, 5 mm. In the latter leads, the associated R wave was usually tall, and the voltage of the Q wave exceeded 25 per cent of the succeeding R wave in only two instances.

Voltage of R Wave.—The maximum, minimum, and mean values are recorded in Table VIII. Since many of the infants and children had electrically vertical

TABLE XI. AMPLITUDE OF

LEADS	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
aV_L	16	2.0	−0.5	0.7	±0.76	16	3.0	−0.5	1.4	±1.1	37	4.0
aV_R	16	−0.5	−0.3	−2.0	±0.81	16	−1.5	−5.0	−2.5	±0.9	37	−1.0
aV_F	16	3.5	0.8	1.6	±0.90	16	4.0	−0.2	1.8	±1.0	37	3.0
V_1	16	−0.5	−4.5	−2.3	±1.2	16	−1.0	−5.5	−2.2	±1.3	35	3.0
V_2	16	0.4	−6.0	−2.4	±2.1	16	3.0	−7.0	−2.6	±2.5	37	3.5
V_3	16	4.5	−5.0	−0.7	±2.2	16	5.0	−5.0	−0.7	±2.8	35	7.5
V_4	16	5.0	−2.5	1.7	±2.3	16	11.0	0	2.4	±2.7	37	9.0
V_5	16	5.5	1.2	2.6	±1.7	16	7.0	0	3.4	±1.7	37	10.0
V_6	16	4.0	0.5	2.2	±1.0	16	5.0	1.5	3.2	±1.3	35	4.5

RS-T Intervals in Seconds

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0.12	0.15	±0.016	14	0.17	0.12	0.14	±0.015	13	0.19	0.12	0.15	±0.021
0.11	0.13	±0.012	14	0.16	0.12	0.14	±0.010	14	0.17	0.12	0.14	±0.013
0.11	0.13	±0.015	14	0.16	0.12	0.15	±0.012	13	0.16	0.12	0.14	±0.013
0.10	0.13	±0.017	14	0.16	0.12	0.14	±0.014	9	0.16	0.12	0.14	±0.014
0.10	0.13	±0.016	11	0.17	0.12	0.14	±0.016	8	0.16	0.11	0.14	±0.025
0.10	0.13	±0.019	8	0.16	0.12	0.13	±0.014	6	0.15	0.09	0.12	±0.020
0.10	0.12	±0.018	9	0.15	0.12	0.13	±0.011	11	0.16	0.12	0.14	±0.012
0.10	0.13	±0.015	12	0.16	0.10	0.13	±0.016	13	0.16	0.12	0.13	±0.014
0.10	0.13	±0.013	14	0.15	0.10	0.13	±0.013	14	0.16	0.12	0.14	±0.014

or semivertical hearts, the R wave in aV_F had the highest voltage compared with the other two unipolar limb leads. It was frequently preceded by a small Q wave and followed by a small S wave. Slurring or notching of the R wave in aV_F was uncommon. In aV_L the R wave was also constantly present, but its voltage was usually not high, and it was not infrequently followed by a deep S wave. The R wave in aV_R was usually small.

In the precordial leads our observations were in accord with the findings reported by Switzer and Besoain.[7] The R wave in V_1 was comparatively small and gradually increased in voltage from V_2 toward the left of the precordium, reaching a maximum in V_4 and then decreasing in V_5 and V_6. The R wave in V_4, V_5, and V_6 was frequently preceded by a small Q wave and followed by a small S wave.

In children under 2 years of age the R wave was rather frequently greater than the S wave in V_1 and V_2.

Depth of the S Wave.—In the unipolar limb leads the S wave was usually deepest in aV_R. In aV_L the S wave might be deep, especially when the heart

T Wave in Millimeters

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
−1.5	0.6	±1.0	16	2.5	−1.0	0.7	±0.7	15	2.0	0.5	0.8	±0.8
−4.0	−2.4	±0.7	16	−0.2	−3.5	−2.0	±1.0	15	−1.5	−4.0	−2.2	±0.7
0.2	1.6	±0.7	16	3.0	−0.2	1.4	±1.1	15	3.5	0	1.3	±0.9
−4.5	−2.3	±1.7	15	1.5	−3.0	−1.7	±1.1	14	0.2	−3.5	−1.3	±1.2
−7.0	−1.6	±2.2	16	5.0	−3.5	0	±2.2	15	3.5	−1.5	0.7	±1.5
−7.0	0.3	±3.1	15	4.5	−2.0	1.8	±2.4	14	5.0	0	1.7	±1.9
−4.0	3.6	±2.6	16	9.0	0	3.2	±2.5	15	7.0	0	3.3	±2.0
0	4.0	±2.0	16	11.0	0.5	4.1	±2.9	15	5.0	1.0	3.1	±1.2
0	2.4	±3.1	15	8.0	0	3.1	±1.9	14	4.0	1.0	2.3	±1.8

was electrically vertical, whereas in aV_F the S wave was usually small. However, the S wave may be absent in any of these three leads, as shown in Table IX.

In the precordial leads, the voltage of the S wave progressively increased from V_1 to V_3 and gradually decreased through V_4, V_5, and V_6. The deepest S wave was usually seen in V_2, V_3, and V_4 (Table IX).

R′ and S′ Waves.—The values of the R′ and S′ waves are not shown because they were infrequently inscribed. The R′ wave may be as high as 5 mm. in aV_R with a complex of either rSr′ or rSR′. In aV_L, V_1, and V_2 the R′ wave was always less than 3 mm. in voltage. No R′ wave was demonstrable in V_4, V_5, and V_6 in the present series.

An S′ wave in one or more leads was inscribed in only six children. This wave, if present, was seen in aV_R, aV_F, and V_1.

RS-T Segment.—Values for the duration of the RS-T segment are given in Table X. It was often difficult to make the measurement in some leads because the RS-T segment was poorly defined. On the whole, the duration of the RS-T segment in a given lead was shorter in infants and younger children than in older children. In the unipolar limb leads the average duration of the RS-T segment was longest in aV_L and shortest in aV_R. In the precordial leads the average duration of the RS-T segment was slightly longer in the right precordial leads (V_1 and V_2) than in the left precordial leads (V_5 and V_6).

Not infrequently the RS-T segment in V_1, V_2, and V_3 was found slightly or moderately elevated. The greatest magnitude of elevation we have seen was 4 mm. above the isoelectric line. The configuration of the elevated RS-T segment, however, was not diagnostic of acute injury current as is seen in cases of myocardial infarction, because the RS-T segment is usually merged with or preceded by a small R′ wave and the convexity of the segment is always downward instead of upward.

In aV_R the RS-T segment may be slightly depressed in some children. Switzer and Besoain[7] also found frequent deviation of the RS-T segment in Leads aV_R, V_1, V_2, and V_3.

T Wave.—Table XI shows the amplitude of the T wave in various leads. In the unipolar leads the T wave was usually positive in aV_F, consistently negative in aV_R, and variable in aV_L.

In the precordial leads the T wave was almost always negative in V_1, especially in children under 4 years of age. It was variable in V_2 and V_3. In V_4 the T wave was diphasic, isoelectric, or positive in most of the children. In V_5 and V_6 the T wave was consistently positive, except for a few instances in which it was isoelectric.

The incidence of a negative T wave in the precordial leads is shown in Table XII, which demonstrates that in a given lead, from V_1 to V_4, negative T waves are less frequent as the children get older.

Q-T Interval.—In the present series of 100 infants and children without evidence of cardiovascular disease, values for corrected Q-T interval ($Q\text{-}T_c$) have been recorded in Table XIII. The maximum $Q\text{-}T_c$ in all age groups was 0.424, and the minimum was 0.365. The mean value was 0.405. No significant

difference in the duration of Q-T_c was found between boys and girls. These observations were in close agreement with the results recently published by Alimurung and associates,[11] with the exception that no variations in different age groups were found.

TABLE XII. INCIDENCE OF NEGATIVE T WAVE IN THE PRECORDIAL LEADS

AGE GROUP (YEARS)	TOTAL NO. CASES	NEGATIVE T WAVE											
		V_1		V_2		V_3		V_4		V_5		V_6	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
I (2 or less)	16	15	94	12	75	9	56	2	13	0	0	0	0
II (2 to 4)	16	14	88	14	88	6	37	0	0	0	0	0	0
III (5 to 7)	37	30	81	22	59	10	27	2	5	0	0	0	0
IV (8 to 10)	16	14	88	6	37	2	13	0	0	0	0	0	0
V (11 to 14)	15	9	60	2	13	0	0	0	0	0	0	0	0
Grand total	100	82		56		27		4		0		0	

Values for the QT/TQ ratio are given in Table XIV. In children under 2 years of age the mean value was 1.5; in those from ages 2 to 4 years, it was 1.2; and in those above 4 years of age, the mean value was less than 1. However, there were great variations in the maximum and minimum values of the QT/TQ ratio in different groups of children. The ratio was observed to vary directly with heart rate with a highly significant correlation ($r = 0.945 \pm 0.011$). In general, when the heart rate is under 100 per minute, this ratio is usually less than one.

COMMENT

It is hoped that the data presented, which are in general agreement with those of other workers, will serve as a normal control for further studies of unipolar electrocardiograms in infants and children of various age groups.

The voltages of the P, R, and S waves were all within the normal limits. The durations of the P-R interval and the QRS complex in infants and children were, on the average, slightly shorter than those in adults.

The presence of Q waves in the unipolar limb and left precordial leads (V_4, V_5, and V_6) is not an infrequent finding in infants and children. The incidence of a measurable Q wave in aV_R and aV_F is higher than in aV_L. This explains why a Q wave in Leads II and III is often demonstrable. The voltage of the Q wave, however, is always less than 25 per cent of the succeeding R wave in aV_F and the unipolar precordial leads. The mechanism of production of the Q wave is most likely by the initial activation of the septum from left to right.

TABLE XIII. DURATION OF

A. Different

	GROUP I (2 YEARS OR LESS)					GROUP II (2 TO 4 YEARS)						
	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM
Boys	9	0.424	0.365	0.403	±0.016	8	0.414	0.385	0.401	±0.013	23	0.417
Girls	7	0.421	0.397	0.405	±0.009	8	0.417	0.383	0.404	±0.011	14	0.417
All	16	0.424	0.365	0.404	±0.013	16	0.417	0.383	0.402	±0.009	37	0.417

B. Entire Age Group

	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
Boys	56	0.424	0.365	0.405	±0.011
Girls	44	0.423	0.383	0.406	±0.009
Total	100	0.424	0.365	0.405	±0.010

The deep Q waves in infants and children have been explained on the basis of the relatively thick ventricular septum and the peculiar position of the heart.[7]

The direction of the T wave in the precordial leads of children has been a subject frequently discussed in the recent literature.[12-18] The T wave in the so-called Lead IV has been found to be negative in many healthy young children. Judging from the results obtained in the present series as well as those reported by other authors in normal infants and children, the negative T wave is usually seen in V_1 and V_2, often in V_3, and sometimes in V_4. The incidence of the negative T waves decreases from the youngest age group to the oldest.

Our data on the Q-T interval compared favorably with those recently reported in a large series of normal children.[11] The establishment of the normal Q-T_c will be helpful for further studies on children with carditis, electrolyte imbalance, and drug therapy (i.e., digitalis, quinidine, and salicylate). The Q-T interval is prolonged in cases with hypopotassemia[19,20] and hypocalcemia[21] and is shortened with digitalis therapy.[22] Taran and Szilagyi[10] have shown that the Q-T interval is prolonged in active rheumatic carditis. This observation has been confirmed by Abrahams,[23] although other investigators[24,25] have been unable to fully verify their findings. Results of our studies in relation to the Q-T_c of many children with or without active rheumatic carditis will be published later.

SUMMARY

Unipolar limb and precordial electrocardiograms were made on 100 infants and children without evidence of cardiovascular disease. The rate, electrical

CORRECTED Q-T INTERVAL

Age Groups

GROUP III (5 TO 7 YEARS)			GROUP IV (8 TO 10 YEARS)					GROUP V (11 TO 14 YEARS)				
MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
0.390	0.405	±0.006	6	0.416	0.389	0.405	±0.010	10	0.423	0.396	0.410	±0.007
0.383	0.406	±0.008	10	0.423	0.392	0.408	±0.012	5	0.420	0.398	0.407	±0.009
0.383	0.405	±0.007	16	0.423	0.389	0.406	±0.011	15	0.423	0.396	0.409	±0.009

position of the heart, and the contour, voltage, and duration of various components of the electrical cycle in each of the nine leads were analyzed and the data summarized in tabular form.

The following points are of special interest:

1. Q waves were frequently seen in Leads aV_R, aV_F, V_4, V_5, and V_6.
2. The T waves were usually inverted in V_1 and V_2, often in V_3, and sometimes in V_4, especially in infants and younger children. The incidence of positivity of the T waves in the precordial leads increased with increasing age.
3. The maximum, minimum, and mean values of corrected Q-T interval, which do not vary with age or sex, are presented. The importance of the establishment of normal value of corrected Q-T interval is discussed.

TABLE XIV. QT/TQ RATIO

GROUP (YEARS)	NO. CASES	MAXIMUM	MINIMUM	MEAN	S. D.
I (2 or less)	16	2.00	1.03	1.50	±0.24
II (2 to 4)	15	1.69	0.72	1.20	±0.23
III (5 to 7)	33	1.54	0.74	0.98	±0.18
IV (8 to 10)	15	1.75	0.66	0.93	±0.28
V (11 to 14)	14	1.55	0.62	0.90	±0.26

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A STUDY OF AUGMENTED UNIPOLAR EXTREMITY LEADS WITH AND WITHOUT 5,000 OHM RESISTANCES IN 500 CONSECUTIVE UNSELECTED PATIENTS

HAROLD I. GRIFFEATH, M.D., AND MAURICE SOKOLOW, M.D.

SAN FRANCISCO, CALIF.

UNIPOLAR leads are being employed widely today in clinical electrocardiography. Opinion differs, however, regarding the exact technique for the recording of unipolar electrocardiograms, and varying methods are in common use.

In 1932, Wilson, Macleod, and Barker,[1] in a preliminary report, described a method of obtaining electrocardiograms that represent the potential variations of a single electrode. This was done by using an indifferent electrode which theoretically had a potential of zero at all times. The indifferent electrode described consisted of a central terminal connected to each of the three extremities (right arm, left arm, and left leg) through noninductive resistances of 25,000 ohms.

In 1934, Wilson and associates[2] described further the method of taking unipolar leads. It was stated that the 25,000 ohm resistances made the apparatus overly sensitive to stray alternating currents. Resistances of 5,000 ohms were finally substituted, which greatly reduced the amount of stray current picked up and proved to be reasonably satisfactory if the skin resistance was kept sufficiently low. It also was stated that the three resistances used in taking unipolar leads must be equal and should be large in comparison with the largest body resistance between any two electrodes.

In 1942, Goldberger[3] wrote that, for purposes of clinical electrocardiography, it is not necessary to equalize the resistances of the circuit by the introduction of fixed resistors, and that the extremities may be joined to a central terminal with ordinary electric wire. He stated that the Wilson assembly employing 5,000 ohm resistances and the Goldberger indifferent electrode with no resistances may be used interchangeably. This opinion, however, has not been universally accepted. The series of cases compared by Goldberger apparently was not large, and slight variations appeared in the illustrated records.

Subsequently, many papers have appeared which discuss various aspects of unipolar lead electrocardiography and the use of resistances.[4-12]

Bryant and Johnston[5] reported a series of 500 patients in which the left arm lead (aV_L) was taken with and without 5,000 ohm resistances. It was stated that a significant difference was found between the curves obtained with the two methods in approximately 10 per cent of the individuals examined. It was

From the Division of Medicine, University of California School of Medicine, San Francisco.
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further stated that the most common variation was a difference in the amplitude of the R deflection, ranging from 2 to 7 mm. in forty-seven individuals. No other variations were mentioned.

Bryant, Johnston, and Wilson[8] reported a study on 500 patients in which aV_L was taken with and without resistances. Differences in P waves, Q waves, R waves, S waves, and T waves were observed. It was stated that the records differed significantly in about one patient out of ten. In the majority of the records which were illustrated, however, the deflections were small, so that very slight variations would represent a manifold difference.

Rappaport and Williams[10] analysed the Wilson and Goldberger methods for registering unipolar leads by the theoretical, mathematical approach. They concluded that "the technique for registering augmented unipolar extremity leads suggested by Goldberger has definite merit, but better results are obtained theoretically if Goldberger's technique is used with the Wilson central terminal."

In view of the problem as presented and the fact that the majority of papers discussing it have used the theoretical approach, it was felt desirable to evaluate the Wilson and Goldberger methods by taking records with and without resistors in a series of consecutive patients.

METHOD OF STUDY

Five hundred consecutive patients referred to the electrocardiographic laboratory of the University of California Hospital were studied. The standard leads and multiple unipolar precordial leads were recorded. In addition, augmented unipolar limb leads were recorded consecutively (a) with the Wilson central terminal containing 5,000 ohm resistances and (b) with the Goldberger modification containing no fixed resistances. The records were taken by experienced electrocardiographic technicians. Special care was taken to ensure adequate preparation of the skin and proper standardization (1 cm. equals 1 mv.). Corrections for standardization were made when necessary. The electrocardiograms taken with and without the resistances were then compared; a magnifying lens was used when necessary. All records were taken with the patient recumbent, in quiet respiration. A Sanborn Instomatic Cardiette was used throughout.

RESULTS

The results of comparing the augmented unipolar limb leads taken with and without 5,000 ohm resistances in 500 patients are summarized in Table I. Four hundred and seventeen individuals (83.4 per cent) showed no difference in the records taken by the two techniques. Sixty-three (12.6 per cent) showed inequalities in the amplitude of the R and S waves as the only difference. In no instance was the difference greater than 3.5 mm., and in the majority (84 per cent) the difference was not over 2 mm. There was no constant relationship between the amplitude of the R or S waves and the presence or absence of resistances. Thirty-nine (62 per cent) showed greater voltage without resistances, and twenty-four (38 per cent) showed greater voltage with 5,000 ohm resistances. In no patient in this group did the difference change the interpretation of the

electrocardiogram from normal to abnormal. Thus, 480 of the 500 individuals showed either no difference in the records or insignificant variations in the amplitude of the R or S waves.

TABLE I. AUGMENTED UNIPOLAR LIMB LEADS WITH AND WITHOUT 5,000 OHM RESISTANCES IN 500 PATIENTS

	CASES	PERCENTAGE
1. No difference	417	83.4
2. Slight differences in amplitude of R or S waves only without any diagnostic significance	63	12.6
3. Definite differences	20	4.0
A. Of interest but without diagnostic significance	14	3
B. Differences conceivably of diagnostic significance	6	1

The remaining twenty patients showed definite differences in the records taken with and without 5,000 ohm resistances. The results are summarized in Table II. In fourteen of these patients, although a definite difference was present, the difference did not change the electrocardiographic interpretation. Many types of variation were seen in this group of "definite differences without diagnostic significance."

TABLE II. CASES IN WHICH DEFINITE DIFFERENCES WERE NOTED WITH AND WITHOUT 5,000 OHM RESISTANCES

Total Cases	20 (4% of original 500)	
1. Changes of interest but without diagnostic significance	14	
A. Change in electrical position only		3
B. Change in amount of ST depression		1
C. Change in depth of Q waves		1
D. Change in QRS pattern of aV_R only		1
E. Change in T waves (see text)		8
2. Changes of possible significance (see text)	6	

1. Three patients showed apparent differences in the electrical position of the heart as determined in the usual manner from aV_L and aV_F. This was due to variation in the size of the R and S waves in these leads. Fig. 1 illustrates such an instance; both records were taken within a few minutes with the patient in the same position.

2. One patient showed greater ST segment depression in aV_L (0.5 mm.) without resistances than with resistances, but this difference was not of diagnostic significance.

3. One patient showed a variation in the Q wave. In aV_L with resistances, a Q wave of 0.5 mm. was present, and without resistances a Q wave of 1.0 to 2.0 mm. was present. The Q wave was sharp and narrow in both instances. The R wave was 6.5 mm. tall in both records. This difference was not considered to be of diagnostic significance.

4. One patient showed a difference in the QRS complex of aV_R only. Without resistances aV_R showed a Q wave of 14 mm. and an R wave of 7 mm., whereas with resistances aV_R consisted of a QS wave of 15 mm. Leads aV_L and aV_F showed no variation.

5. In eight patients there were definite T-wave differences, but the differences were not of significant magnitude to influence the electrocardiographic interpretation.

In three patients the total QRS voltage was 3.5 mm. or less. Since the T wave in aV_L may normally be inverted when the R wave is small, no diagnostic significance could be attached to these changes.

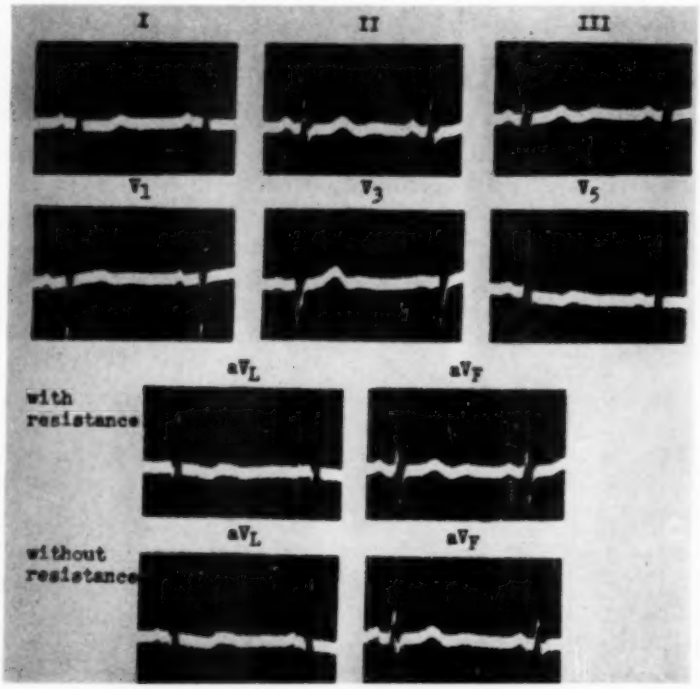

Fig. 1.—J. W., a woman 60 years old. Hypertension with moderate cardiac enlargement. Note the more horizontal position revealed with resistances.

In one patient aV_L showed a minute T wave (0.3 mm.) with resistances and an isoelectric T wave without resistances. This change was considered not of sufficient magnitude to be significant.

In one patient the T wave in aV_L was inverted by both methods but slightly more inverted without resistances.

In three patients the T waves showed minor differences in aV_F. Fig. 2 illustrates such an instance.

The six remaining patients showed differences of possible significance.

1. B. L. S. showed a difference in aV_L (Fig. 3). The R wave was 5 mm. in both records. The T waves were low upright to slightly diphasic with resistances and diphasic to slightly inverted without resistances. Minor differences in the T wave in aV_F also occurred.

This patient was a 51-year-old man with substernal pain of three years' duration, not definitely from angina.

2. D. R. showed a difference in aV_L (Fig. 4). With resistances there was an R wave of 6 mm., no S wave, and a T wave of plus 0.5 mm. Without resistances there was an R wave of 5 mm., no S wave, and an inverted T wave of minus 0.5 mm. After exercise, the T wave in aV_L was more deeply inverted when the

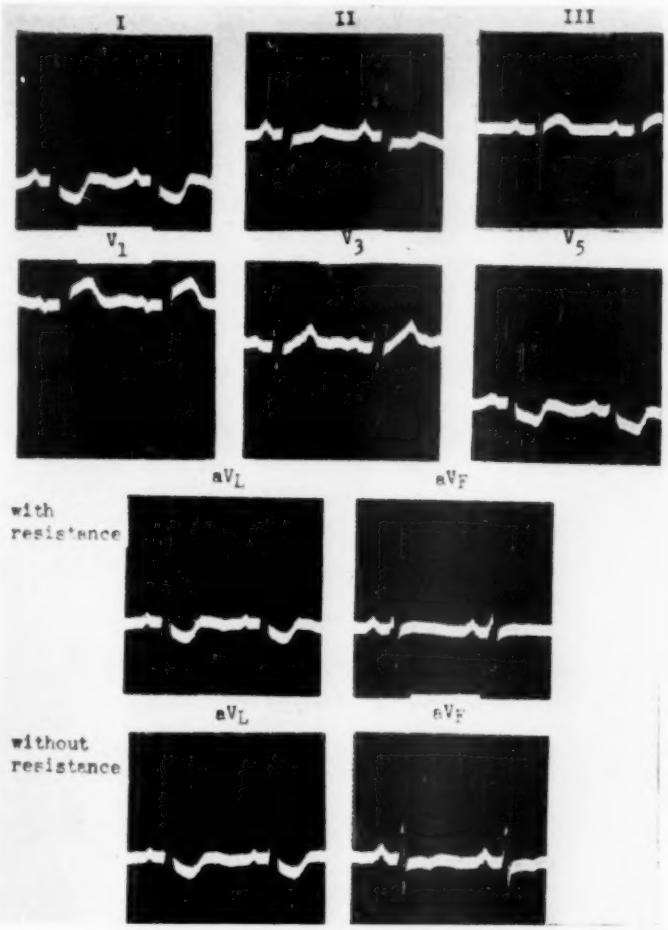

Fig. 2.—A.M., a woman 56 years old. Hypertensive cardiovascular disease with congestive failure treated with digitalis. Note the slight difference in the T wave in aV_F; the T wave is low diphasic without resistances and flat with resistances.

resistances were omitted. In this patient, the T wave in aV_L could be interpreted as borderline abnormal without resistances. This finding is considered borderline abnormal rather than definitely abnormal because of the relatively low R wave of 5 mm.

This patient was a 34-year-old woman with essential hypertension. Her blood pressure was recorded as 240/120 mm. Hg, and the lowest level obtained

with the Sodium Amytal test was 160/112 mm. Hg. The heart was within normal limits of size by x-ray examination.

3. F. R. showed changes in aV_L (Fig. 5). With resistances there was an R wave of 4 mm. and a T wave which was slightly inverted. Without resistances the R wave was 7 mm. and the T wave was flat to minimally diphasic. The slightly inverted T wave in aV_L with an R wave of 4 to 5 mm. would not be called

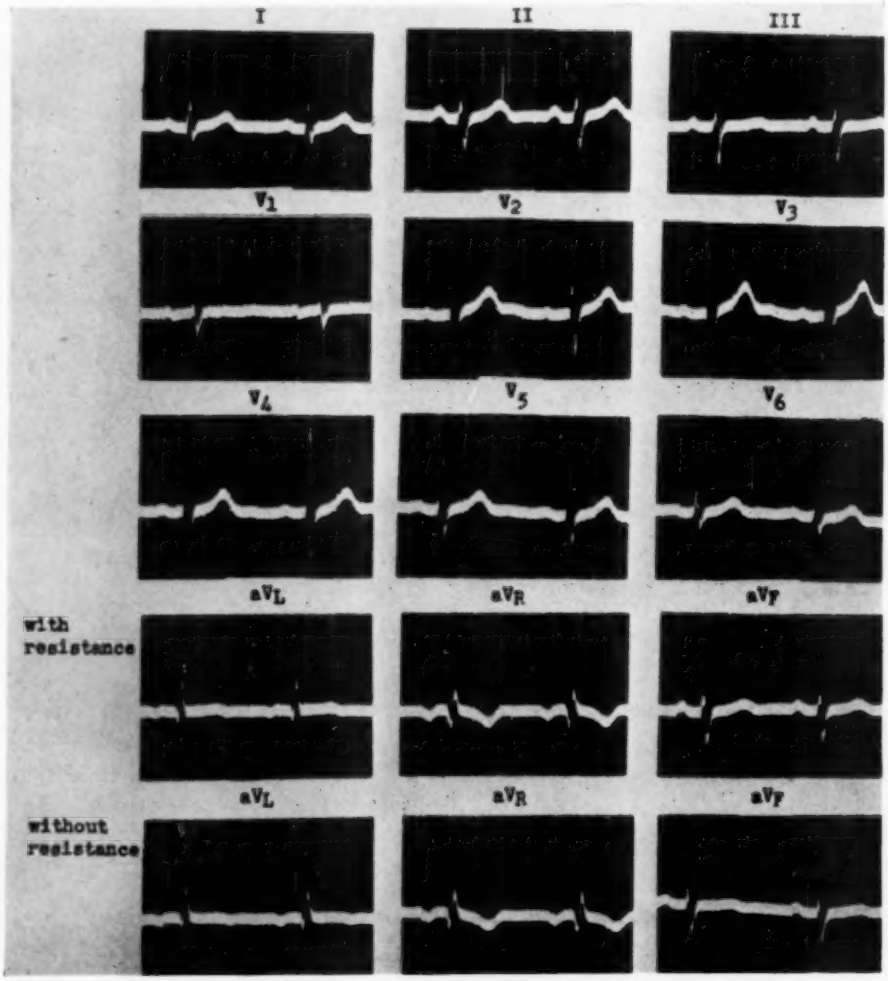

Fig. 3.—B. L. S., a man 51 years old. Substernal pain of three years' duration, not definitely angina pectoris. T in aV_L without resistances is slightly more diphasic than that in aV_L with resistances.

definitely abnormal because of the low amplitude of the R wave. However, this was a borderline finding, and aV_L was more abnormal with resistances than without resistances.

This 47-year-old woman had hypertension with cardiac failure, requiring frequent mercurial injections as well as digitalis therapy and sodium restriction.

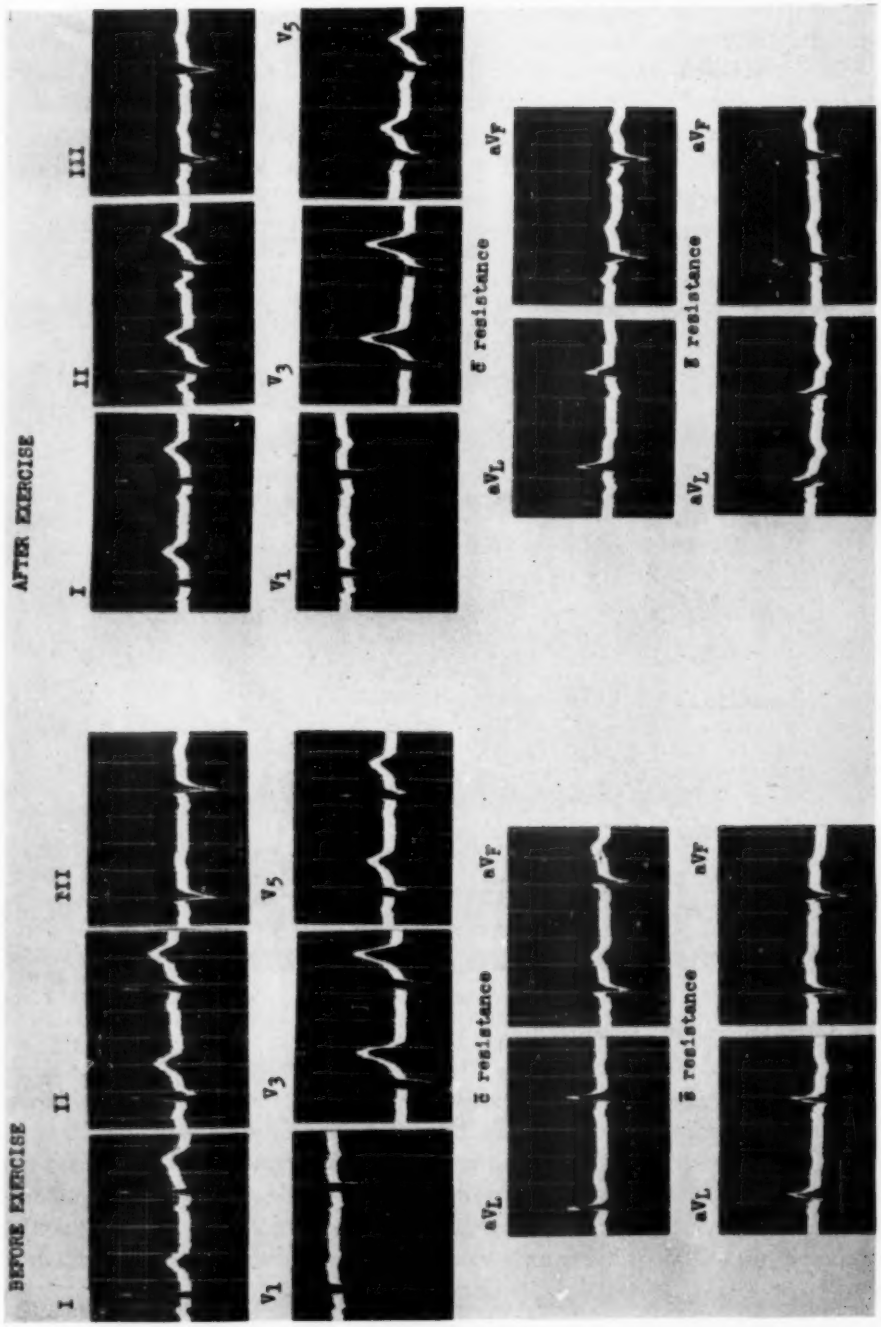

Fig. 4.—D. R., a woman 34 years old. Hypertension. Left chest ache not considered angina pectoris. Note that the T wave is slightly inverted in aV_L without resistances, whereas it is low uprightwith resistances.

4. F. D. showed a flat T wave in aV_L with resistances but a diphasic T wave without resistances. The ventricular complex in aV_L without resistances resembled aV_F, V_5, and I (Fig. 6). This woman, 45 years old, had syphilitic aortic insufficiency with congestive failure requiring treatment with digitalis.

5. R. D. showed a difference in aV_L. With resistances, there was an R wave of 5 mm. and a T wave of plus 0.5 mm. Without resistances, there was an R wave of 5 mm. and a T wave which was flat to slightly inverted. This represents a change in the contour of the T wave in aV_L from normal with resistances to borderline abnormal without resistances.

This patient was a 60-year-old man who had possible coronary heart disease and an anxiety tension state.

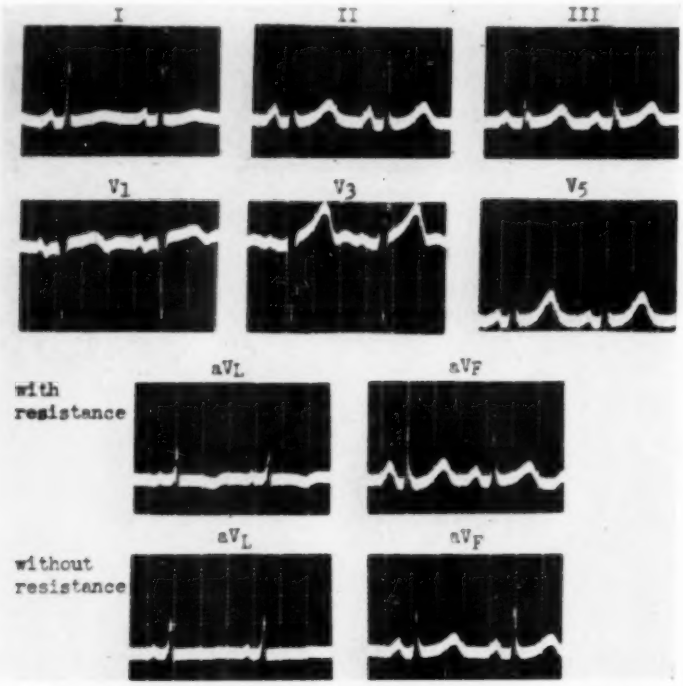

Fig. 5.—F. R., a woman 47 years old. Hypertensive cardiovascular disease with congestive failure. Note that the T wave is slightly inverted in aV_L with resistances, whereas it is essentially flat in aV_L without resistances.

6. S. G. showed a variation in aV_L. With resistances as well as without, the R wave was 8 mm. tall, and there was no S wave. The T wave, however, was 0.75 mm. tall with resistances and flat to plus 0.25 mm. without resistances.

This patient was a 68-year-old woman with a clinical diagnosis of arteriosclerotic heart disease. She had episodes of paroxysmal auricular tachycardia and a blood pressure varying from 160 to 192 systolic and 86 to 110 diastolic.

DISCUSSION

The differences in the augmented unipolar extremity leads taken with and without 5,000 ohm resistances were usually unimportant and were not always

in the same direction. Only 4 per cent or twenty of the series of 500 unselected patients demonstrated definite differences with or without resistors; six or 1 per cent of the entire group revealed differences that might have been of diagnostic significance. Study of these six patients indicated that most of these possibly significant changes were limited to variations in the T wave in aV_L. The differences, with or without the 5,000 ohm resistances, varied between a low upright or diphasic T wave and a slightly inverted T wave. In no case did the difference in the T wave with and without resistances exceed 1 mm., and in all six patients the R wave in aV_L was relatively low, varying between 4 and 8 mm. in height.

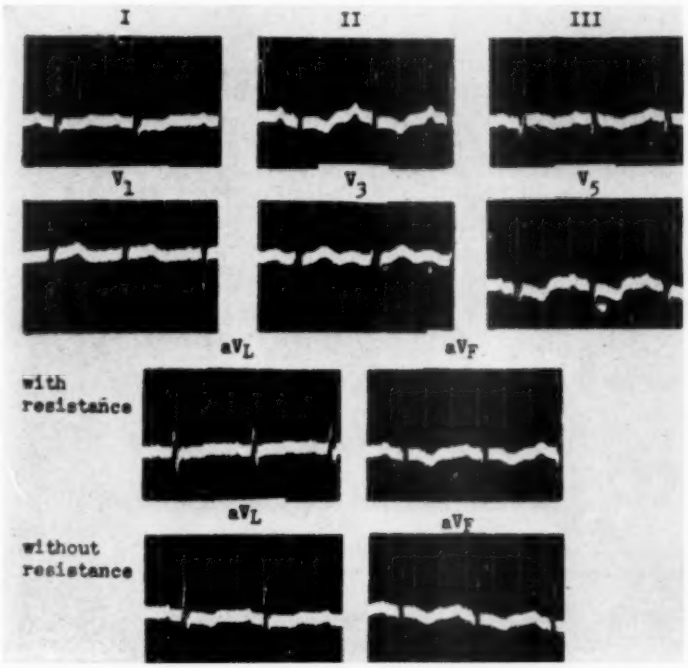

Fig. 6.—F. D., a woman 45 years old. Syphilitic aortic insufficiency with congestive failure and digitalis treatment. The T wave is slightly inverted in aV_L without resistances and essentially flat in aV_L with resistances.

Figs. 3 and 4 illustrate the findings in two patients in whom the T wave in aV_L was more abnormal when resistances were omitted, but Fig. 5 reveals that in one patient the T wave was more normal in aV_L when resistances were omitted.

On theoretical grounds, the use of 5,000 ohm resistances is preferable because variations in skin resistance at the several extremities might affect the electrocardiographic patterns. In the present series of patients, particular care was taken by experienced technicians to decrease skin resistance by careful application of the electrodes, after scraping the skin with a tongue blade and then applying electrode jelly. It is apparent that when this care is taken, no significant diagnostic errors are likely to occur in most patients. For ordinary clinical use either method can be used, although resistances are advised to minimize the possible "artifacts" produced by variations in skin resistance.

SUMMARY AND CONCLUSIONS

1. Augmented unipolar limb leads with and without 5,000 ohm resistances were taken consecutively in 500 unselected patients referred to the electrocardiographic department.

2. In 96 per cent of the patients there was either no difference in the records or insignificant variation in the amplitude of R or S waves.

3. In 4 per cent of the patients definite differences in the records were present. Many types of variation were observed, including differences in P waves, Q waves, R waves, S waves, ST segments, and T waves. In the majority of these, however, the difference was of no diagnostic significance and was not always in the same direction.

4. In six patients, or 1 per cent of the total group, differences were found which were of possible diagnostic significance. The maximum difference was between a T wave in aV_L that might be interpreted as a normal or a borderline finding or between a borderline and an abnormal finding.

5. For purposes of clinical electrocardiography, augmented unipolar extremity leads taken either with or without 5,000 ohm resistances will prove satisfactory in the majority of patients, providing particular care is taken in the preparation of the skin and the application of the electrodes.

6. The use of 5,000 ohm resistances is preferable because of possible variations in skin resistances if the resistors are omitted.

We are grateful to Mrs. Doris Tuttle, Miss Nancy Gelardi, and Miss Angie Galante for their technical assistance.

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THE EFFECT OF DIGITOXIN ON THE V LEADS

ROBERT BEERS, M.D., WILLIAM REGAN, M.D., AND
JULIUS JENSEN, M.D.

ST. LOUIS, MO.

IT IS well known that digitalis produces changes in the electrocardiogram when given in sufficient dosage.[1] These changes are largely associated with the process of repolarization. Considerable literature exists concerning this effect on the conventional leads I, II, III, and the CF leads.[2,3,4] In general, the findings indicate downward changes in the RS-T segment and gradual depression of the T waves, which tend first to become flattened, then diphasic (− +), and finally entirely inverted. Some of these changes resemble those associated with hypertrophy and ischemia resulting from impaired coronary circulation.

Relatively little has been written concerning the effect of digitalis on the V leads. Yet these offer a new opportunity to study in detail this effect on the various parts of the heart. Until now, it has not been clear whether the digitalis effect always follows the same pattern and whether the effect on the myocardium is general or focal. Nor has a clear differentiation been made in these leads between the digitalis and other RS-T and T changes. This study was undertaken to contribute to our knowledge of the effect of digitalis on the individual parts of the heart as recorded in the V leads.

METHOD

Fifty patients were studied. Four were admitted partially digitalized; forty-six had received no digitalis during the previous month. Twenty-eight had normal cardiovascular findings; twelve were classified as having hypertension (systolic blood pressure of 170 mm. Hg or higher or diastolic blood pressure of 100 mm. Hg or higher); three had auricular fibrillation; four were diagnosed as having degenerative or arteriosclerotic heart disease because of congestive failure, cardiac enlargement, or electrocardiographic changes. Three patients fell into a miscellaneous group: one had leucemia and electrocardiographic changes (leucemia infiltration of myocardium?); the second (a 38-year-old man) had T-wave inversion extending from V_1 to V_4 but no other evidence of heart disease; and the third had a history of extrasystoles.

The patients varied in age from 18 to 95 years, and all were admitted to Missouri Baptist Hospital between February and July, 1950. Four were admitted as cardiac patients with congestive failure; in the others the cardiac findings were incidental.

From the Medical Service of the Missouri Baptist Hospital, St. Louis.
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Digitoxin (Crystodigin, Eli Lilly and Company, Indianapolis, Ind.) was administered by mouth with one exception. The initial dose was 0.6 mg. followed by 0.4 mg. daily until the patients became nauseated or left the hospital, or until the drug had to be discontinued for other reasons. Altogether, eighteen patients received between 1.0 and 1.9 mg., sixteen received between 2.0 and 2.9 mg., and twelve received between 3.0 and 4.0 mg. In four cases the exact amount was not determined because these patients had been partially digitalized prior to admission. A control electrocardiogram was taken before digitoxin was given and in most cases daily thereafter. The leads used were aV_R, aV_L, aV_F, and V_1 through V_6. These were then mounted for easy analysis.

FINDINGS AND CONCLUSIONS

The analysis of the material fell into two parts: (1) the study of the actual changes following digitoxin, and (2) the relation of these changes to the clinical findings.

Changes.—The electrocardiograms were studied in detail, viz., the rate, rhythm, the P wave, P-R interval, QRS complex, RS-T segment, and the T wave.

The rate was slowed in thirty-six patients, faster in ten, and unchanged in four. In those unchanged and faster the dosage exceeded 1.4 mg. in all cases. The over-all slowing was 5.4 beats per minute. The findings are suggestive, but not conclusive, that digitalis slows the ordinary sinus rate when given in moderate doses.

The rhythm remained constant with two exceptions. In one there was a history of previous extrasystoles; in the other auricular fibrillation was present, and, as the rate slowed, extrasystoles appeared.

The P wave was unchanged, while the P-R interval lengthened 0.01 to 0.04 second as might be expected.[5,6] The QRS complex also remained constant. Chief interest was focused upon the RS-T and T changes. These are classified in Tables I and II.

TABLE I. RS-T CHANGES

	ELEVATED RS-T	DEPRESSED RS-T	NO CHANGE
aV_R	43	0	5
aV_L	11	24	15
aV_F	1	37	12
V leads	1	44	5

It will be noted from this table that the RS-T segment is generally elevated in leads from the endocardial surface and depressed in leads from the epicardial surface. It was further noted, though not stated in the table, that this applies also in the V leads in both left-sided and right-sided patterns. In only one patient was the RS-T segment elevated over the right precordium. Here it occurred in Leads V_2 and V_3 after 1.0 mg. of digitoxin had been given. The next two days, after 1.4 mg. and 2.0 mg., respectively, had been received, the

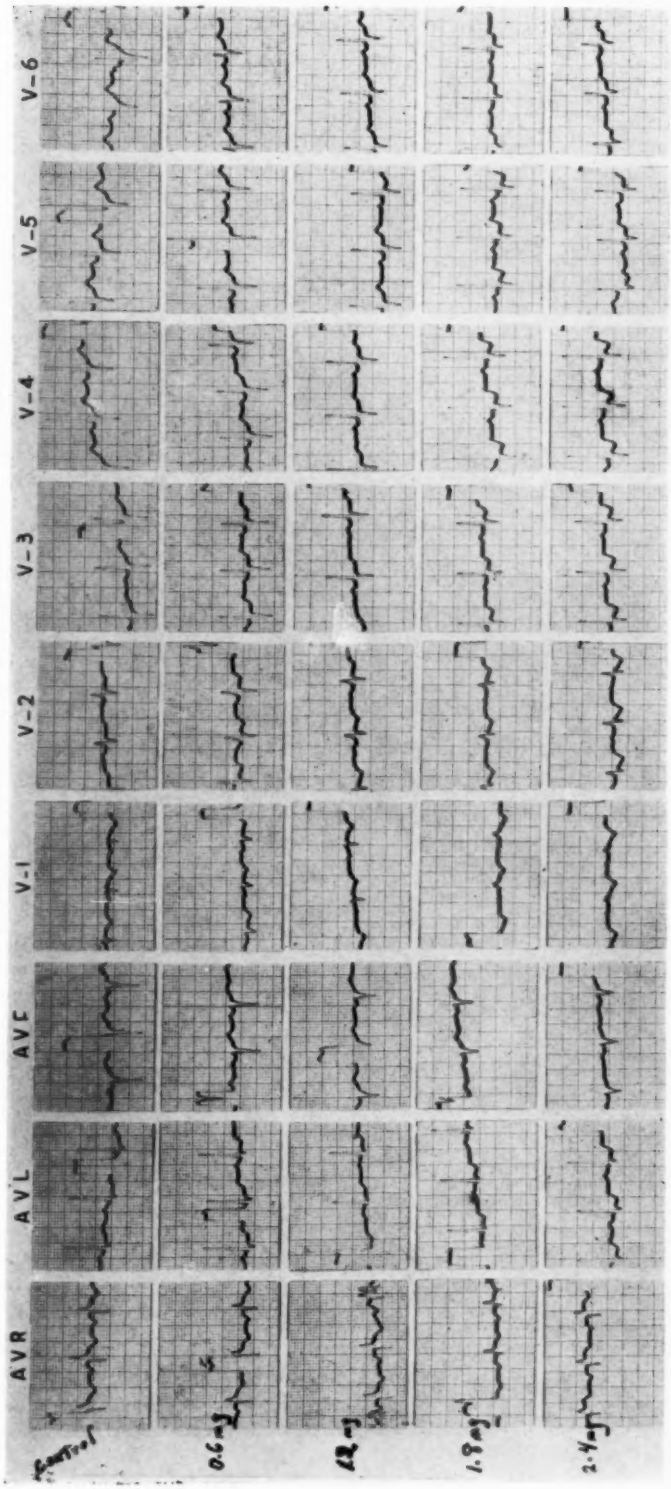

Fig. 1.—Illustrating the changes of digitalization in a horizontal heart. The RS-T is elevated in aVR, depressed in aVL, and depressed in the V leads. Note the lowered RS-T take-off in the chest leads and the most prominent changes in those leads over the left ventricle. The tracings were taken at daily intervals.

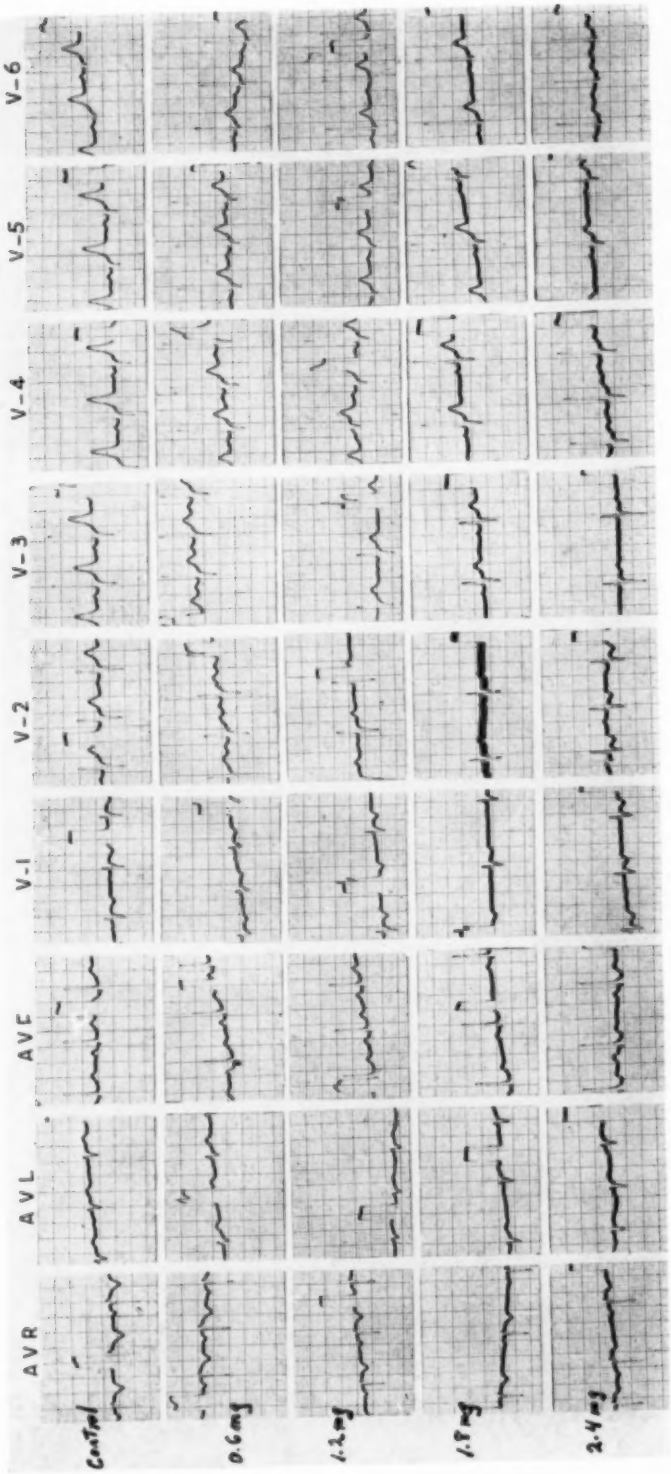

Fig. 2.—Illustrating the electrocardiographic changes following digitoxin administration in the vertical heart. RS-T in aV_R is again elevated; it is also elevated in aV_L, but depressed in the V leads. The most marked RS-T and T changes are in V_1, V_2, and V_3. The tracings were taken at daily intervals.

RS-T segment again returned almost to the isoelectric line. It was not, therefore, an instance of severe permanent digitalis effect.

The most consistent change in the RS-T segment demonstrated was an elevation in aV_R (90 per cent). The next most consistent change was depression in the V leads (88 per cent), and the third was depression of RS-T in aV_F (74 per cent). As can be seen by reference to Table I, changes in aV_L were variable. Elevation or depression in this lead was related directly to the position of the heart. In the eleven patients with elevation of RS-T, the heart was vertical in nine; and of the twenty-four with depression of RS-T, sixteen were in the horizontal position. Patients showing no change received 1.4 mg. or less over three days.

Forty-five patients developed sagging and/or depression of the RS-T segment. It is of interest to note that in thirty-one of the fifty the RS-T takeoff was actually depressed at least 1 mm. and in many, 3 to 4 mm.

The T-wave changes were more variable. Sometimes the amplitude of the T waves increased, later to decrease under larger doses. These changes are, therefore, somewhat difficult to classify.

In aV_R the normal inversion of the T wave persisted in all cases. In forty-five patients the T-wave amplitude lessened, in four it became deeper, and in only one could no change be noted. The leads taken from the epicardial surfaces of the heart were classified as shown in Table II.

TABLE II. T-WAVE CHANGES

	LESSENED AMPLITUDE	INCREASED AMPLITUDE	NO CHANGE
aV_L	26	18	6
aV_F	38	7	5
V_{1-6}	45	4	1

The changes were quite diverse, the lessened amplitude varying from a slight lowering of the T wave to a diphasic or inverted appearance.[7] Here again, roughly the same changes prevailed over both the right and left precordium. In general, the changes were most conspicuous over the left, but in a smaller number of cases the changes were more marked over the right precordium. An attempt was made to correlate the type of change with the electrical position of the heart (Table III).

TABLE III. RELATION OF RS-T AND T-WAVE CHANGES TO POSITION OF THE HEART

	VERTICAL	INTERMEDIATE	HORIZONTAL
Right precordial changes	5	2	1
Left precordial changes	7	5	15
No focal pattern demonstrable	5	3	1
No changes noted	1	1	4

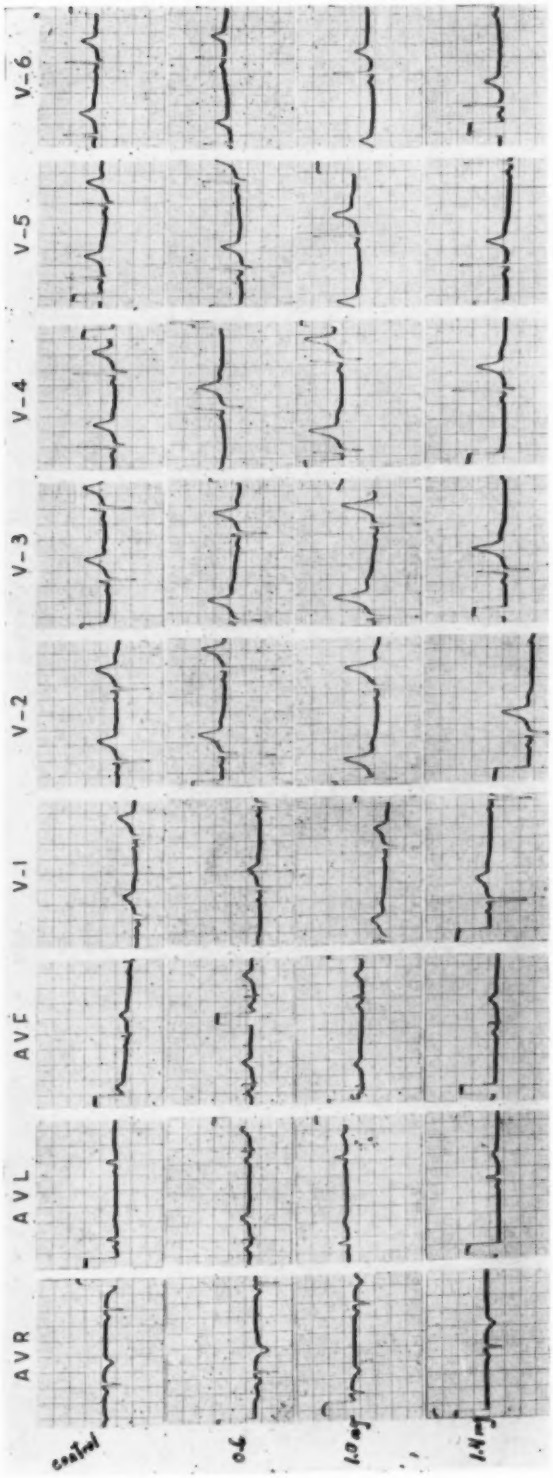

Fig. 3.—This figure is included to demonstrate the increased amplitude and transient pointing of the T waves following small doses of digitoxin. They are most pronounced in the transitional V_2, V_3, and V_4 leads. The tracings were taken at daily intervals.

It is apparent from Table III that digitalis manifests itself most markedly over the left precordium in the horizontal heart and to a lesser extent over the right precordium in the vertical heart.

In relation to dosage, two types of changes were noted, some early and transitory after a small dose, others later and more profound. In a number of patients on whom daily tracings were taken, it was noted that on the second or third day, after 0.6 to 1.0 mg. had been given, changes occurred which later disappeared. Of twenty-eight patients studied in this manner, the changes were noted in eighteen. They consisted of lessened amplitude of the T waves in the general region of V_2 and V_3, followed by a secondary rise, and then a depression. Occasionally, it was noted further to the right or left or even in aV_L. In three patients there was also a tendency to transient "pointing" of the T wave. This occurred most commonly after 0.6 mg. had been given and disappeared after 1.0 mg. Occasionally, it took a larger dose of digitoxin to produce it. This apparently involved a relatively small mass of muscle, for there was never any significant change in aV_R. If more extensive muscle mass had been involved, change should have been noted in this lead, reflecting as it does the sum total of cavity potential. In a number of patients this change was quite slight, but in others it was unquestionable.

Relation to Clinical Data.—An attempt was made to correlate the age, sex, and size of the patients with the amount of digitoxin required to produce changes in the electrocardiogram. No relationship was noted. Apparently other factors are more important than size, age, or sex.

It has been stated that digitalis was more prone to cause changes in hearts which were already the site of latent or manifest lesions.[8] Accordingly, our material was divided into two groups, the patients who had heart disease and those whose cardiovascular system was apparently normal. In the first group were placed the twenty-two patients previously described as abnormal, in the second the twenty-eight normal patients. The amount of digitoxin required to produce the electrocardiographic changes in the former was no different than in the latter. It should be stated that profound RS-T depression and T-wave inversion were demonstrated only in the four patients who had received small amounts of digitalis over a long period and were then pushed to clinical toxicity in this series.

DISCUSSION

Several observations were impressive during this investigation. One was the relatively slight electrocardiographic change observed, considering the amount of digitalis given. While 1.2 mg. of digitoxin is generally considered a full digitalizing dose,[9,10] in every case we exceeded this amount, in many patients by 200 to 300 per cent, over a short period of time. Often, the digitoxin produced nausea and vomiting (supposedly a late toxic effect),[11] and yet the electrocardiogram showed only moderate RS-T depression and some lowering of the T wave. This would make one wonder whether the striking changes do not require digitalis therapy over an extended period of time, advanced myocardial pathology with

hypertrophy, or a peculiar susceptibility of the patient. We would suggest that the time element and the muscle mass are important requisites in the profound changes.

Another impressive finding was the rare appearance of cardiac arrhythmias. Premature contractions, bigeminy, trigeminy, tachycardia (of auricular, nodal,[12] or ventricular[13] origin), auricular fibrillation, auricular flutter, partial and complete heart block,[6] and electrical alternans[14] are various arrhythmias previously reported.[11] We found the appearance of ventricular extrasystoles in two patients; in the other forty-eight there was no change in the basic rhythm.

The relation of the augmented and V leads to the more conventional limb and CF leads is as one would expect. We noted consistent RS-T elevation in aV_R. This shows itself as RS-T depression in Leads I and II and is accentuated whenever there is RS-T depression in aV_L and aV_F, recording the same effect from the epicardial surface. Therefore, the standard limb leads may show digitalis in a more accentuated manner than the augmented unipolar limb leads. This is not true in the V leads as compared with the CF leads. Here, the changes registering over one epicardial surface are deducted from those registering over another epicardial surface. With the RS-T and T waves changing in the same direction in each and being recorded as algebraic differences, they will tend to cancel one another in the CF leads. It is apparent from this brief discussion that the digitalis effects can be shown more accurately in the V leads than in the bipolar electrocardiogram.

One perplexing problem in the study of cardiology is the differentiation between the effects of digitalis and the effects of heart disease as recorded by the electrocardiogram.[15,16] Two conditions which are fairly common and produce confusion are left ventricular strain and anterior myocardial infarction. Left ventricular strain, particularly when associated with hypertrophy, shows RS-T depression and T-wave inversion in the left precordial leads, which may be mistaken for digitalis effect.[10] The take-off is depressed; there is a cove-shaped rise followed by the inverted T. aV_L and aV_F when registering a preponderantly left ventricle will do likewise.[17] The RS-T and T in aV_R may become elevated.[18] With digitalis the RS-T take-off is depressed in the same leads, but there is no tendency toward coving, rather a flattened straight downward slope toward an inverted T. The T-wave changes may be impossible to differentiate.[18] However, with digitalis the QRS complexes are not increased in amplitude or widened, and the Q-T interval is shortened rather than prolonged.

In acute anterior infarction the elevation of RS-T in aV_R with decrease in amplitude of T and depression of RS-T in the other limb leads may mimic the effects of digitalis, but in the acute stage there is marked elevation of the RS-T segment in the precordial leads.[19] This is, of course, in contradistinction with the digitalis changes as recorded in this paper. Later, when there are T-wave changes which resemble each other, the RS-T has returned to the isoelectric line, and a deep Q is present. With digitalis, when the T is finally inverted, there is RS-T depression; also, the appearance of a deep Q wave has never been attributed to digitalis. Electrocardiographic findings should correlate with clinical data whenever possible.

SUMMARY

The effect of digitoxin on the V leads was studied in fifty patients. Twenty-eight were healthy, and twenty-two had various forms of heart disease.

The principal effects were in the RS-T and T segments. In general, there was a tendency for the RS-T segments to become elevated in the leads registering cavity potential and depressed in the leads from the epicardial surface of the heart. In a few patients there was a transitory tendency for the T wave to become tall and pointed, but, in general, it became lower or inverted. In the V leads this change was most marked in the left precordial leads when the heart was in the transverse position, and over the right precordial leads when it was in the vertical position.

In addition, there was noted over the center of the precordium a tendency to transient T-wave change, which disappeared as the dosage was further increased. While this change was slight in many patients, in some it was unmistakable.

Notwithstanding the fact that digitalis was given in full doses, even to the point of vomiting, it was impressive that the changes noted were relatively slight. It is suggested that the striking changes seen in patients with advanced heart disease receiving digitalis require for their production pre-existing heart disease, digitalis administered over a long period of time, or a peculiar susceptibility of the patient.

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REPORT ON A NEW MERCURIAL DIURETIC, CUMERTILIN, BRAND OF MERCUMATILIN

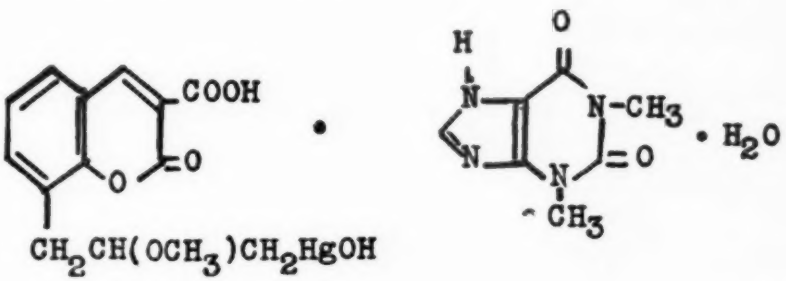
LOUIS H. SIGLER, M.D., AND JOSEPH TULGAN, M.D.

BROOKLYN, N. Y.

THE diuretic value of any mercury compound is gauged by the amount of urine it eliminates, by the rapidity of such elimination, and by the presence or absence of any untoward or toxic effects. With these indices in view, a comparison was made of the effects of a new mercurial diuretic, Cumertilin,* with another currently available mercurial diuretic, Mercuhydrin. The latter compound was selected for comparative study because, like Cumertilin, it can be used for intramuscular injection with little or no local reaction.

Cumertilin, according to the manufacturers, is a synthetic compound containing 27.9 per cent mercury. It is supplied in sterile aqueous solution, each cubic centimeter containing approximately 39 mg. of mercury and 50 mg. of theophylline, adjusted to a pH of about 7.3. Its formula is 8-(2′ methoxy − 3′ hydroxy-mercuri propyl) − coumarin − 3 carboxylic acid . theophylline.

It differs from other available diuretics in that the allyl group is attached to a ring carbon atom of a heterocycle instead of being in the form of an allylamide. The better effects and increased stability of the compound, as claimed by the manufacturers, are due to the mercurated C-allyl group in contrast to the mercurated N-allyl groups in other preparations. Its structural formula is:



We have used this drug in 9 ambulatory and 8 nonambulatory patients with cardiac decompensation with approximately the same diuretic effects in both groups. Because of the longer periods of observation of the ambulatory group, which offered a better opportunity for comparing the effects of this drug with those of Mercuhydrin, the results with the 9 ambulatory patients are reported in detail.

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*The Cumertilin was supplied by Dr. Samuel M. Gordon, Endo Products, Inc., Richmond Hill, N. Y.

In order to study the specific effect of this mercurial compound, no other drug, such as ammonium chloride, that has a tendency to increase diuresis, was given at the same time.

SELECTION OF CASES

The 9 ambulatory patients were carefully selected as to their intelligence, reliability, and willingness to cooperate in every detail as to the use of a salt-poor diet, the passage of urine at regular periods, and careful measurement and recording of each urinary excretion. They were under our observation for a period of 1 to 3 years before this study, during which time they required a weekly injection of Mercuhydrin to keep them comfortable. Three of them had rheumatic and 6 arteriosclerotic heart disease. Five were women and 4 men. The 3 rheumatic patients were 35, 40, and 56 years old, respectively, and the 6 arteriosclerotic patients ranged in age between 60 and 73 years.

METHOD OF STUDY

Alternate injections of 2 c.c. of Mercuhydrin and Cumertilin were given intramuscularly at weekly intervals. The patient did not know, of course, which drug was used at any time, so as to eliminate any possible psychologic effect. The first specimen of urine was passed about 2 hours after the injection, and the subsequent 6 specimens were passed as close to hourly intervals as possible. The rest of the specimens were passed as per urge till the end of 24 hours.

The time of passage of each specimen of urine and the amount passed were recorded by the patient, and his record was brought to the clinic on his next visit. A separate, detailed summary sheet was kept at the clinic for each patient, covering the entire period of observation of 8 to 14 weeks. An analysis was then made of the amount of urine passed by each patient the first 24 hours after the given injection and the average amount passed during the first 24 hours for the entire period of observation. The latter was determined by adding all the urine passed under the given drug during the entire period of observation and dividing it by the number of injections. Similarly, the average amounts passed during the first 8 hours and the hourly passages were determined.

OBSERVATIONS

The urinary output during the first 24 hours on different days and under the different drugs is shown in Table I.

It will be observed that there is considerable variation in the response to both diuretics in different individuals and in the same individual on different days. In general, however, the response appears to be on the average somewhat greater under Cumertilin than under Mercuhydrin. If we take, for instance, patient M. P., who showed the lowest response to both diuretics, the maximum output under Mercuhydrin was 50 ounces in 24 hours, whereas under Cumertilin it was 54 ounces. Patient D. E. showed the greatest response to both drugs. The maximum output under Mercuhydrin was 103 ounces and under Cumertilin

136 ounces, with a difference of as much as 33 ounces. In patient M. S. the average response appeared to be in favor of Mercuhydrin. The maximum output on any one day under Mercuhydrin in this patient was 98 ounces and under Cumertilin 95 ounces. Even in this patient, however, the minimum output was greater under Cumertilin than under Mercuhydrin, being 77 and 70 ounces, respectively. One patient, S. C., appeared to show a persistently greater response to Mercuhydrin during a period of 8 weeks in which the 2 diuretics were used. In this patient the response to either drug was not very good except on 2 occasions when the elimination in 24 hours was 92 and 83 ounces, respectively. On both these occasions, the greater output occurred under Mercuhydrin. The period of observation in this patient, however, was shorter than in the other patients.

TABLE I. COMPARATIVE AMOUNTS OF URINARY OUTPUT IN OUNCES IN 24 HOURS UNDER THE GIVEN DRUG

DRUG	M. S. F 61	D. E. F 40	E. V. F 35	M. P. F 56	M. T. F 61	S. C. M 64	H. M. M 62	D. S. M 68	G. S. M 73
Mercuhydrin	93	94	51	29	94	76	82	74	50
EN 564	88	92	40	46	71	70	95	91	109
Mercuhydrin	79	87	61	42	92	64	58	61	72
EN 564	77	100	58	54	63	62	75	110	89
Mercuhydrin	70	103	64	50	52	92	52	89	90
EN 564	95	116	76	54	65	60	63	78	114
Mercuhydrin	82	86	81	34	68	83	64	83	62
EN 564	78	136	69	31	99	60	74	71	100
Mercuhydrin	98		67	43			39	94	66
EN 564	86	112	71	37	63		44	82	92
Mercuhydrin			53	25			42	81	83
EN 564		97	81				37	72	95
Mercuhydrin							52	86	93
EN 564			76				32	85	90

Initials above each column = name of patient; F = female, M = male; number next to F or M = age in years.

"EN 564" was the original term used by the manufacturer for Cumertilin.

The average composite output under the 2 drugs for the entire period of observation in each patient is shown in Table II. It will be observed that only in patients M. T. and S. C. was the response in favor of Mercuhydrin. All other patients showed a somewhat greater average 24 hour urine output under Cumertilin. The combined average 24-hour output for the entire group was 71.4 for Mercuhydrin and 75.8 for Cumertilin.

More important than the total 24-hour output is the output in the first 8 hours after the injection. With the exception of patient E. V., where the response was the same under both drugs, it was persistently higher in all other patients under Cumertilin than under Mercuhydrin, as shown in Table II. It was true even in patients M. T. and S. C. where the 24-hour output was greater under Mercuhydrin. The average 24-hour output in these patients under Mercuhydrin was 76 and 79 ounces for M. T. and S. C., respectively, and under Cumertilin 72 and 63 ounces, respectively. The first 8-hour output, however,

was 38 and 48 for Mercuhydrin and 42 and 53 for Cumertilin. The percentage output in these patients in the first 8 hours under Cumertilin was, therefore, 8.3 per cent greater in patient M. T. and 23.4 per cent greater in patient S. C. than under Mercuhydrin.

TABLE II. AVERAGE URINARY OUTPUT IN OUNCES

PATIENTS	UNDER MERCUHYDRIN			UNDER CUMERTILIN		
	AVERAGE 24 HOURS	AVERAGE FIRST 8 HOURS	PER CENT IN 8 HOURS	AVERAGE 24 HOURS	AVERAGE FIRST 8 HOURS	PER CENT IN 8 HOURS
M. S.	84	40	48.0	85	47	55.3
D. E.	93	55	59.1	109	61	55.9
E. V.	63	25	39.6	67	25	37.3
M. P.	37	24	64.8	44	30	68.2
M. T.	76	38	50.0	72	42	58.3
S. C.	79	48	60.7	63	53	84.1
H. M.	56	38	67.8	60	45	75.0
D. S.	81	41	50.6	84	44	52.4
G. S.	74	42	56.7	98	44	44.9
All patients combined	71.4	39.0	54.6	75.8	43.4	57.2

The general output in 8 hours under Mercuhydrin varied between 24 and 55 ounces, ranging between 39.6 per cent and 67.8 per cent of the 24-hour output. Under Cumertilin the output varied between 25 and 61 ounces in the first 8 hours with a percentage of 37.3 per cent and 84.1 per cent. The average output the first 8 hours for the entire group was 39.0 ounces under Mercuhydrin and 43.4 ounces under Cumertilin, with a percentage of the 24-hour output of 54.6 per cent and 57.2 per cent, respectively.

Of the 8 nonambulatory patients, 2 were in the late phases of congestive heart failure with anasarca and chronic indurative edema of the lower extremities. These 2 patients responded very poorly to all mercurial diuretics, and the response to Cumertilin was also poor. The maximum 24-hour output was about 25 ounces. One of the patients had an output of 40 ounces under Cumertilin after aspiration of a massive ascites. The other 6 patients had an elimination of 50 to 120 ounces in the first 24 hours under Cumertilin. The percentage output the first 8 hours varied between 50 and 75 per cent of the 24-hour output.

UNTOWARD EFFECTS

No serious untoward or toxic effects were observed in most of the 9 ambulatory and the 8 nonambulatory patients after the injection. Patient G. S., who received 7 injections of Cumertilin, complained on one occasion of slight pain at the site of injection, probably due to injury of a nerve by the needle. Patient H. M., who also received 7 injections, had severe pain on one occasion, and on another occasion a lump developed at the site of the injection, probably due to a

deep-seated hematoma caused by an injury of a vessel by the needle. The other 5 injections were not associated with any discomfort. Patient M. T., however, who received 5 injections, had experienced on one occasion a headache and pain at the site of injection, on another occasion nausea and vomiting, and on a third and a fourth occasion marked pain at the site of injection, radiating to the leg. Patient D. E., who received 6 injections, showed a papular rash at the site of the injection on one occasion. The other 5 injections gave no disturbances. One nonambulatory patient complained of a warm sensation all over the body for about 10 minutes after an intravenous injection of Cumertilin. Another nonambulatory patient developed some muscular cramps several hours after the injection, the same as after the injection of other mercurials that she had received.

Thus, of the 75 injections given to 17 patients, reactions occurred on 10 occasions, 3 of which were more than local and quite disturbing.

SUMMARY AND CONCLUSIONS

A preliminary report on a new mercurial diuretic, Cumertilin, is presented. The drug was used on 17 patients with cardiac decompensation, 9 ambulatory and 8 nonambulatory. Although the number of patients from which to draw definite conclusions is small, the diuretic effects of the drug appear to be at least equivalent to another mercurial diuretic with which it is compared. Also, with few exceptions, the drug appears to be well tolerated.

CONGENITAL TRICUSPID ATRESIA

SHELDON C. SOMMERS, M.D., AND J. MARTIN JOHNSON, M.D.

DETROIT, MICH.

PRIMARY isolated tricuspid atresia has heretofore been considered one of the rarest congenital cardiac anomalies. The condition is characterized by the absence of a right atrioventricular opening with associated interauricular and interventricular septal defects. Hypoplasia of the right ventricle is a constant finding. Since the establishment of a department of pediatric cardiology* at Henry Ford Hospital, six instances of isolated tricuspid atresia have been encountered among 141 autopsied patients with congenital heart disease (Table I). This experience has prompted reporting the six cases with a critical review of the literature on the subject.

Abbott,[1] in her analysis of 1,000 cases of congenital heart disease, gave eleven examples of this anomaly. We have excluded the cases of Burdach[2] and Cathala and Tesserand[3] because there were right atrioventricular openings in these patients, although the tricuspid valves were defective. Among 132 cardiovascular anomalies, Dry and associates[4] found one tricuspid atresia. Pertinent pathological findings in the thirty-one acceptable cases reviewed are summarized in Table II. It appears that a number of other cases have been observed.[32-35] Instances complicated by transposition of the great vessels, pulmonary atresia, or other major abnormalities have been excluded from consideration.

CASE REPORTS

CASE 1.—C. J. F. (A-4908), a 6-month-old white female infant, had been constantly cyanotic since birth at term and was markedly underdeveloped. Cyanosis had gradually increased until admission to the hospital. No past or family histories were available. Examination revealed a thrill in the left third interspace and a loud basal systolic murmur. On fluoroscopy the left ventricle was markedly enlarged; the electrocardiogram showed left axis deviation. When the heart was catheterized, the right ventricle could not be entered. The red blood cells numbered 3.5 million per cubic millimeter. Other routine laboratory findings were normal. Before cardiac treatment could be instituted, the child aspirated the stomach contents and died of asphyxia.

At autopsy the heart weighed 25 grams. The right atrium was slightly dilated, and its wall measured 0.1 cm. in thickness. There was a well-defined Chiari's network. The atrial floor was smooth without any communication with the right ventricle (Fig. 1,*A*). An oval defect, 1.8 cm. in greatest diameter, was present in the posterior interatrial septum and was divided medially by a thin fibrous band. The left atrium was normal in size and thickness. There was a Y-shaped incompetency of the mitral valve. The left ventricle was markedly enlarged, and its wall was thickened to 1.0 cm. with a slitlike defect, 0.4 cm., high in the interventricular septum. The right

From the Department of Pathology, Henry Ford Hospital, Detroit.
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*Under the direction of Dr. Robert F. Ziegler.

ventricle was hypoplastic and appeared as an appendage in the left ventricular wall. Its outer wall averaged 0.4 cm. thick (Fig. 1,*B*). The pulmonic and aortic valves were normally formed, and each measured 2.8 cm. in circumference. The major arterial calibers corresponded to their valves. The ductus arteriosus was closed. Other findings included aspiration of vomitus and marked passive congestion of all viscera.

TABLE I. MAJOR AND ASSOCIATED CARDIOVASCULAR ANOMALIES IN 141 AUTOPSIED PATIENTS

	MAJOR	ASSOCIATED
Septal Defects		
Interauricular	2	2
Patent foramen ovale	13	16
Interventricular	21	31
Tetralogy of Fallot	21	
Eisenmenger complex	3	
Interauricular and interventricular	21	6
Cor biloculare	6	
Valve Anomalies		
Tricuspid atresia	6	
abnormal		5
Pulmonic atresia	1	4
stenosis	4	26
bicuspid	2	2
tetracuspid		1
Mitral abnormal	3	1
Aortic atresia	1	2
stenosis		2
bicuspid	3	3
absent	1	
Infundibular stenosis	2	2
Reticulated leaflets	6	
Vessel Anomalies		
Transposed great vessels	10	3
Patent ductus arteriosus	6	12
Aortic coarctation	2	6
Misplaced coronary ostia	1	4
Venous anomalies		5
Peritracheal vascular ring		1
Miscellaneous		
Von Gierke's cardiopathy	3	
Idiopathic hypertrophy	1	
Dextrocardia	1	4
Unclassified	1	
Total	141	

CASE 2.—G. D. (A-5313), also a 6-month-old white female infant, was admitted to the hospital for severe bilateral acute otitis media. She had shown constant cyanosis since birth, progressively more severe in the past two months. She was born of a primiparous full-term uncomplicated pregnancy without a family history of congenital anomalies or diseases. On physical examination there was a loud apical systolic murmur. The red blood cell count was 3.9 million per cubic millimeter. Before further studies could be done, the child became more dyspneic and cyanotic and died on the third hospital day.

At autopsy the heart weighed 55 grams. The wall of the right atrium was 0.2 cm. thick, and the superior vena cava entered at an angle so that the blood flow was directed toward the auricular appendage. The foramen ovale had a well-developed valve with a scalloped border and several thin marginal attachments. There was no right atrioventricular communication, and only a small

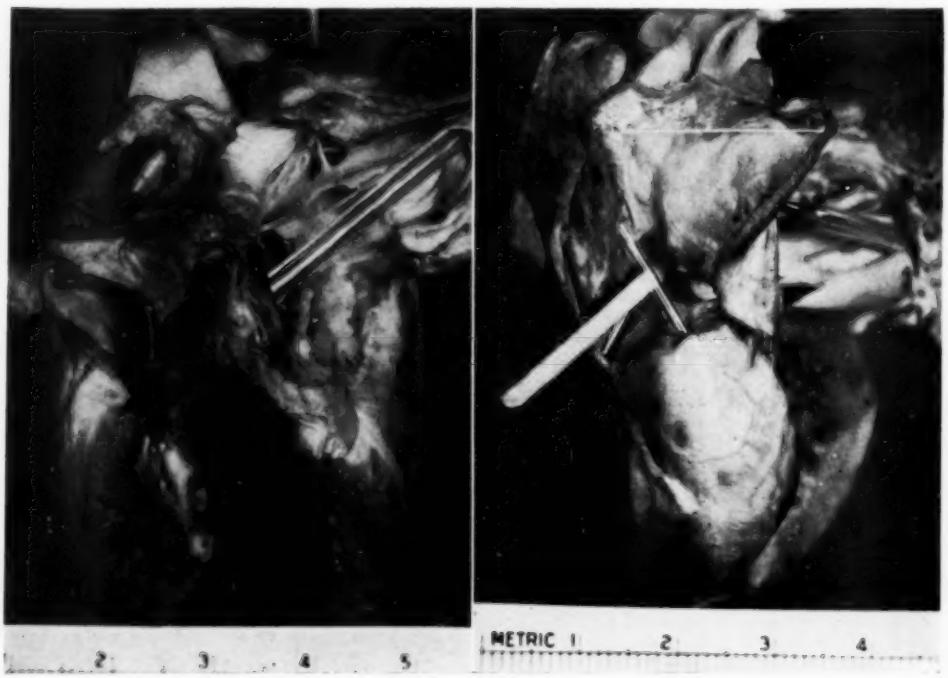
TABLE II. REPORTED CASES OF CONGENITAL TRICUSPID ATRESIA

		SEX	AGE	FORAMEN OVALE VALVE	PULMONIC VALVE		DUCTUS ARTERIOSUS	REMARKS
					STENOSIS	LEAFLETS		
1	Sieveking[5]	*	9 wk.		Yes	Normal		
2	Kelly[6]	*	5 mo.	None	No	Normal	Open	
3	Barlow[7]	F	11 wk.		Yes	Two cusps joined, frenum	Open (?)	Ectopia lentis, mitral vegetations, aortic coarctation, transposed great vessels (?)
4	Crocker[8]	M	9 mo.	Cordlike	Marked	Three cusps adherent	Closed	
5	Chapotot[9]	M	20 mo.	None	No	Normal	Closed	Scarlatinal pneumonia
6	Aschoff and Schreiber[10]	M	2½ yr.	Complete, thick	Yes	Two cusps adherent	Small, open	Obliterative pericarditis, mitral vegetations, passive congestion
7	Cohn[11]		16 mo.	Complete	Yes, 1.8 cm.‡	Normal	Closed	Valved interventricular defect
8	Bernstein[12]	M	2⅔ yr.	None		Normal	Closed	Ball-valve thrombus in interventricular defect
9	Kühne[13]		14 mo.	Present	Yes, 2.5 cm.	Normal	Closed	
10	Kühne		9 mo.	None	Yes, 2.3 cm.	Bicuspid	Closed	
11	Nuhn[14]	M	6 wk.				Closed	
12	Hiffe[14]	*	4 mo.		No			
13	Henriette[14]	F	5 yr.	Incomplete	Yes		Closed	Mitral vegetations
14	Wieland[15]	F	6 mo.	Incomplete	No, 1.7 cm.	Normal	Small, open	
15	Hess[16]	M	8½ mo.		Yes	Normal	Small, open	
16	Huebschmann[17]	M	5 mo.	Incomplete	Yes	Bicuspid	Almost closed	Mitral and aortic valves tetracuspid
17	Huebschmann	M	5½ mo.	Incomplete	Yes	Bicuspid	Almost closed	Pulmonary artery course posterior
18	Mönckeberg[18]	F	8 mo.	Incomplete	Yes	Bicuspid	Closed	Family history of albinism
19	Rihl and co-workers[19]		7 mo.	Fenestrated	Yes, 2.0 cm.	Bicuspid	Closed	Congenital syphilis, mitral valve tricuspid, conus endocarditis

20	Breslich[20]	M	9 mo.	Fenestrated	Yes, 1.5 cm.	Bicuspid	Small, open	
21	Blackford and Hoppe[21]	M	8 mo.	Incomplete	Yes, 1.8 cm.	Bicuspid	Closed	
22	Bellet and Stewart[22]	F†	4¼ yr.	Fenestrated	Yes, 3.0 cm.	Normal	Closed	One small aortic leaflet
23	Murphy and Bleyer[23]	M	4 mo.	Incomplete	Yes, 2.0 cm.	Normal		
24	Grayzel and Tennant[24]	F	10 hr.	Complete	Yes, 1.0 cm.	Normal	Open	Coronary ostia in pulmonary artery, abnormal coronary sinus, aortic branch to lung
25	Brown[25]	M	8 mo.	Incomplete	No	Normal	Closed	
26	Hammond[26]	†	7 mo.	None	Yes	Bicuspid	Closed	
27	Holder and Pick[27]	F	10 mo.	Rudimentary	Yes	Bicuspid, granular	Open	Valved interventricular defect
28	Alexander and White[28]	M	5½ mo.	Incomplete	Yes, 0.75 cm.	Normal		Mitral valve tricuspid, misplaced coronary ostia, Blalock operation
29	Taussig[29]	F	4¼ yr.	None	No, 3.5 cm.	Normal	Closed	Infundibular stenosis
30	Dry and associates[4]	F	4 mo.	Present	Yes	Bicuspid	Closed	Cerebral sinus thromboses
31	Miale and co-workers[30]	F	3⅓ yr.	Incomplete	No	Fibrous	Closed	Right otitis media, brain abscesses

*Male, according to Vierordt.[31]
†Negro infant.
‡Circumference of pulmonic valve.

round depression in the atrial floor (Fig. 2,*A*). The left atrium and the mitral valve were normal. The left ventricle was large, and its wall was 0.8 cm. thick. High in the interventricular septum was a defect, 0.8 cm., communicating with a hypoplastic right ventricle, whose wall measured 0.4 cm. in thickness. The pulmonic valve was normally formed and measured 2.2 cm. in circumference (Fig. 2,*B*). The aortic valve also was normal and measured 3.2 cm. in circumference. The pulmonary artery and aorta had the same respective circumferences as their valves. The ductus arteriosus was closed. There were moderate passive congestion of liver and spleen and multiple small emboli throughout the viscera.



A. B.

Fig. 1 (Case 1).—*A*, Right atrium, held open by a glass tube, above which is the Chiari's network. The large left ventricle is below with the incompetent mitral ostium visible. *B*, Hypoplastic right ventricle with probe in the interventricular septal defect. The upper glass rod holds open the pulmonic valve.

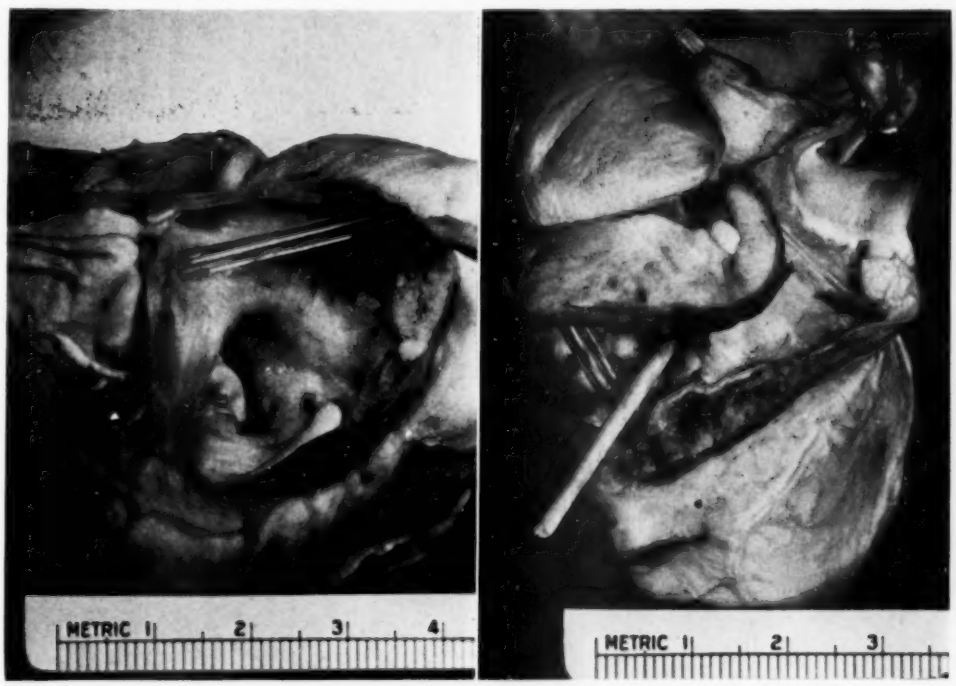
CASE 3.—E. N. (A-5333), a 5-month-old white female infant, at 2 months of age, began having intermittent attacks of cyanosis, which became progressively more frequent and severe. At the time of admission to the hospital, moderate cyanosis was constant. On examination no thrill was found, but there was a precordial systolic murmur with wide transmission. Fluoroscopy revealed marked left ventricular enlargement, and the electrocardiogram showed left axis deviation. The red blood cell count was 4.3 million per cubic millimeter, and the remaining routine laboratory work was normal. A left Potts[32] anastomosis was done which relieved the cyanosis, but the child died of congestive heart failure on the eighth postoperative day.

At autopsy the heart weighed 50 grams. The right atrium was slightly dilated with a wall 0.2 cm. in thickness and a reticulated Chiari's network. There was no right atrioventricular communication. The foramen ovale was closed, but there was a triangular defect with sides measuring 0.3 cm. in the posterior interauricular septum (Fig. 3,*A*). The left atrium and the mitral valve appeared normal. The left ventricle was dilated, and its wall measured 1.0 cm. thick. There was a small irregular defect, admitting an 0.5 cm. probe, high in the interventricular septum opening into the hypoplastic right ventricle. The pulmonic valve was bicuspid, but it measured

2.1 cm. in circumference, and the pulmonary artery had the same caliber (Fig. 3,*B*). The aortic valve was 2.6 cm. and the aorta 3.0 cm. in circumference just above the valve. The ductus arteriosus was closed. There were bilateral pleural effusions and marked passive congestion of abdominal viscera.

CASE 4.—S. P. (A-5354), a 10-month-old white female infant, had had constant and progressive cyanosis from the age of 3½ to 7½ weeks, at which time a left Blalock operation was done at another hospital. Her postoperative course was uneventful, but mild cyanosis persisted, and she did not gain weight normally. There was one sibling alive and well. The mother was Rh negative, and the father and child Rh positive, but the pregnancy had been quite normal.

She was first seen at this hospital at the age of 4½ months with a rough systolic murmur over the left third and fourth interspaces, a continuous murmur with systolic accentuation over the operative site, and corresponding thrills. The red blood cell count was 4.0 million per cubic millimeter. The digits were not clubbed. At the age of 9½ months she developed congestive heart failure and died after twenty days of hospitalization.



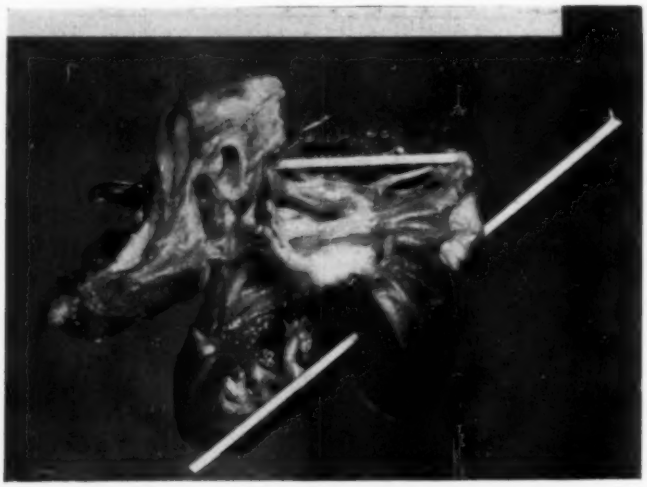
A. B.

Fig. 2 (Case 2).—*A*, Right atrium seen from above. The superior vena caval ostium is immediately above the glass tube, and below it is the imperforate atrial floor. The patent foramen ovale opens to the left. *B*, View of right ventricle, pulmonic valve, and probe in the interventricular septal defect.

At autopsy the heart weighed 90 grams. The right atrium measured 0.2 cm. in thickness. The superior vena cava entered it at an angle which diverted the blood flow toward the right auricular appendage. The right atrioventricular valve ostium was absent and the atrial floor smooth. The foramen ovale was covered by a folded membrane, but in the posterior interatrial septum there was a 1.0 by 0.3 cm. slitlike opening (Fig. 4,*A*). The left atrium and the mitral valve were normal. The left ventricle was dilated, and its wall measured 0.9 cm. in thickness. It communicated with the hypoplastic right ventricle through a slit, 0.7 cm., high in the interventricular septum. The wall of the right ventricle was 0.6 cm. thick. The pulmonic valve was bicuspid and measured 1.2 cm. in circumference. The pulmonary artery was of the same size (Fig. 4,*B*).

There was a right aortic arch, and the aortic valve and aorta were large, measuring 3.2 cm. in circumference. The right coronary ostium originated behind the right posterior cusp. The ductus arteriosus was closed, and the Blalock anastomosis was patent. In addition, there were recent intracranial hemorrhage and chronic passive congestion of the lungs and abdominal viscera.

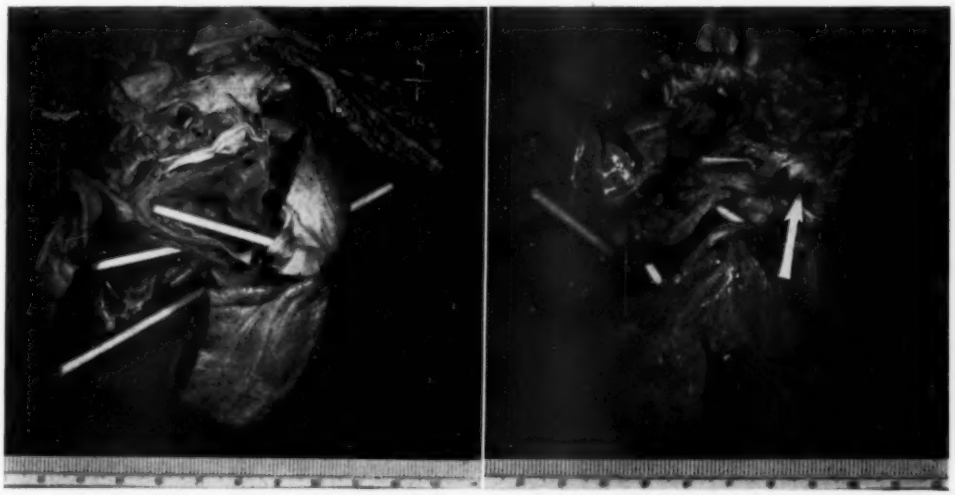
CASE 5.—S. C. (A-5494), a 4-month-old white female infant, was hospitalized for mild constant cyanosis with intermittent severe attacks which were becoming more frequent. She was born of a full-term uncomplicated pregnancy. There was a 3-year-old sister alive and well. Physical examination showed moderate cyanosis and a precordial systolic murmur. On fluoroscopy the



A.

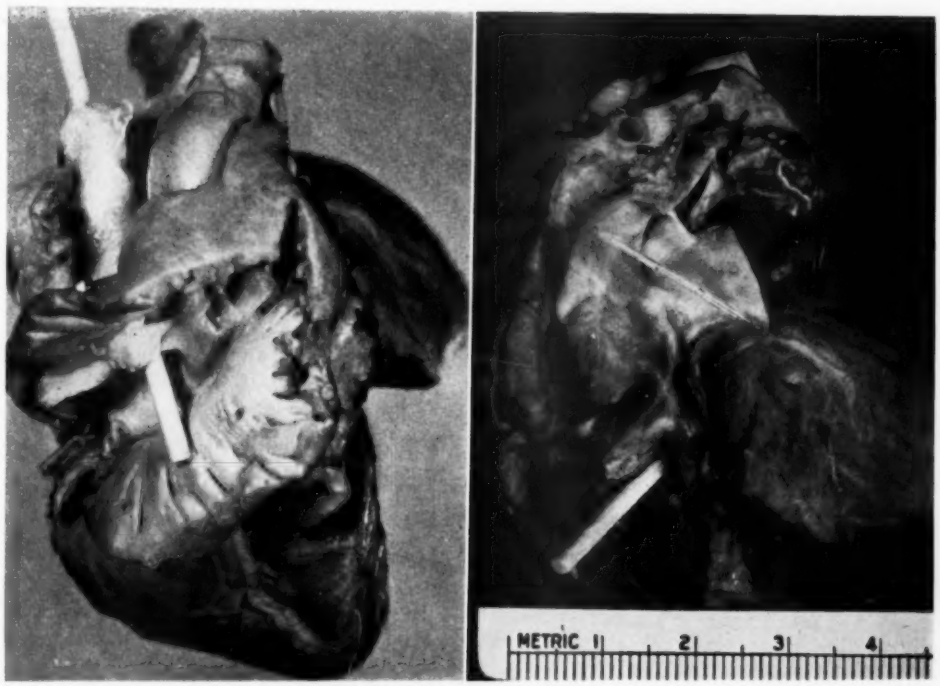
B.

Fig. 3 (Case 3).—*A*, Opened right atrium with Chiari's network. The long probe passes through the interventricular septal defect. *B*, Anterior view of small right ventricle with a probe in the interventricular defect. Note the bicuspid pulmonic valve. The Potts anastomosis site is visible where the opened aorta bends sharply.



A. B.

Fig. 4 (Case 4).—*A*, Right atrium is held open by a rod, above which the superior vena caval opening lies. The long probe traverses the interventricular septal defect. *B*, Right ventricle, with a probe through the interventricular defect, and bicuspid pulmonic valve. The arrow indicates the Blalock anastomosis.

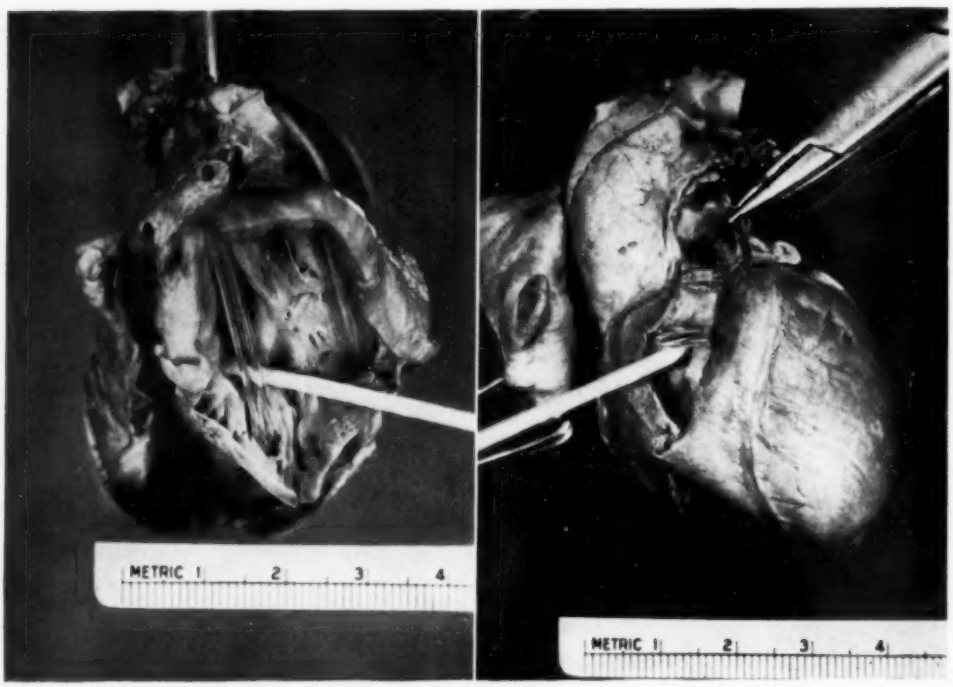


A. B.

Fig 5 (Case 5).—*A*, The opened right atrium is seen with a probe in the superior vena cava. The persistent right sinus venosus valve is stretched over the probe. *B*, Hypoplastic right ventricle with a probe in the interventricular opening. Below the glass rod is the pulmonic valve.

heart was enlarged to the left, and the electrocardiogram showed left axis deviation. The red blood cell count was 5.7 million per cubic millimeter, and other routine laboratory studies were normal. A left Potts operation was done with relief of the cyanosis, but the child died of esophageal rupture two weeks later.

At autopsy the heart weighed 50 grams. The right atrium measured 0.2 cm. in thickness, and there was a persistent right sinus venosus valve. The foramen ovale had a well-developed leaflet and a patency 0.7 cm. in greatest diameter. There was no right atrioventricular communication (Fig. 5,*A*). No abnormality of the left atrium or the mitral valve was seen. The left ventricle was dilated, and its wall was 0.7 cm. thick. There was an oval defect 0.5 cm. in diameter high in the interventricular septum through which blood could pass into the small right ventricle. The right ventricular wall was 0.5 cm. thick (Fig. 5,*B*). The pulmonic and aortic valves were each tricuspid, 3.0 cm. in circumference, and their respective vessels were of the same size. The ductus arteriosus was closed, and the anastomosis, 0.5 cm. in length, was patent. The entire esophagus was necrotic and in its lower third had ruptured into the posterior mediastinum and right pleural space.



A. B.

Fig. 6 (Case 6).—*A*, Right atrium with superior vena caval orifice above and midway between the glass rods. The probe is in the posterior interatrial septal defect. *B*, Right ventricle with probe through the interventricular septal defect. The fleshy pulmonic valve is just below the clamp.

CASE 6.—L. G. (A-5513), a white female infant 3 months old, had been constantly cyanotic since birth, with periods of marked cyanosis and respiratory distress accompanying any increased activity. She was born after a normal nine-month pregnancy. There was one sibling alive and well at 3½ years of age. Examination revealed a well-developed and well-nourished child, moderately cyanotic with frequent attacks of severe respiratory embarrassment. There was a soft precordial systolic murmur. The heart was small by roentgenogram. The electrocardiogram showed left axis deviation. The red blood cell count was 4.79 million per cubic millimeter.

In the hospital frequent episodes of severe cyanosis and anoxia continued, and she died on the fifth hospital day.

At autopsy the heart weighed 43 grams. The superior vena cava entered the thickened right atrium at an angle directed toward the auricular appendage. The wall of the atrium measured 0.3 cm. in thickness, and there was no right atrioventricular communication. There was a slitlike opening, 0.4 by 1.0 cm., in the posterior interauricular septum. The foramen ovale was closed (Fig. 6,*A*). The left atrium and the mitral valve appeared normal. The left ventricle measured 0.7 cm. in wall thickness. A semilunar slit, 1.5 by 0.2 cm., in the interventricular septum communicated with the right ventricle which had a wall 0.4 cm. thick. The pulmonic valve had three thickened cusps and was 1.2 cm. in circumference, as was the pulmonary artery (Fig. 6,*B*). The aortic valve measured 2.6 cm. and the aorta 2.7 cm. in circumference. The ductus arteriosus was closed. Aspiration of stomach contents and passive congestion of the lungs and abdominal viscera were also noted.

EMBRYOGENESIS

The customary theories of the origin of tricuspid atresia are that during the partitioning of the heart, there is displacement of the interauricular septum primum and septum secundum,[15,20,21] the interventricular septum,[18] or the endocardial cushions[21] so far toward the right as to close the primitive right atrioventricular ostium. While difficult to disprove, such theories have little support from observations of the embryologic or pathologic features. The process of cardiac partitioning is quite complex and influenced by many factors.[36,37]

In Cases 2, 4, and 6 the superior vena cava entered the right atrium after crossing the heart base from the left side and appeared to represent a persistent left superior vena cava, as described in two previous cases of tricuspid atresia.[26,27] It did not empty into the coronary sinus, which had a separate ostium in the usual position, unlike the left superior vena caval anomaly most often reported.[38] This abnormality originates embryologically in the sinus venosus at about 28 days ovulation age, the earliest traceable anomaly encountered in our patients.[39]

Cases 1, 3, 4, and 5 had Chiari's network or persistence of the right sinus venosus valve,[40] reported in one previous case.[27] These structures develop at about 35 days ovulation age[37] and are rarely found after birth.

The effect of each or both of these anomalies would be to direct the superior vena caval blood stream toward either the auricular appendage or foramen ovale, respectively. Normally, in the embryo the superior vena caval flow is directed at the tricuspid ostium which it may serve to keep open.[41] Gross and microscopic examinations of the right atrial floor in our patients revealed small crypts or fibrous bands in four at the site of tricuspid atresia. Since in all thirty-seven cases reported the patients had right ventricles, a right atrioventricular orifice must once have existed, despite abnormal intracardiac blood currents.

The pulmonic valve was bicuspid in twelve patients from thirty-seven collected tricuspid atresia cases. The valve leaflets are formed about the thirty-fifth day of ovulation age and are influenced by blood currents.[37] This is supplemental indirect evidence of pre-existent abnormal blood currents in the right ventricle and pulmonary artery. The presence and degree of pulmonic stenosis have been emphasized, but they appear largely secondary to the size of the interventricular septal defect. Twenty-five of thirty-seven patients had smaller pulmonic rings compared to the aortic valve circumference, which may be enlarged. Similarly,

the interatrial and interventricular defects normally do not close until later in embryonic life,[42] and persisting patencies may reasonably be ascribed to abnormal intracardiac blood currents already established.

Tricuspid atresia has not been reported as hereditarily transmitted in siblings or in offspring following maternal rubella or following experimental noxae in animals. Histologic study of the present patients provided no evidence of previous inflammation or fetal endocarditis. As a frequently isolated mechanical anomaly in an otherwise normally formed infant, tricuspid atresia may be explained satisfactorily mechanically.

CLINICOPATHOLOGIC CORRELATIONS

A clinical diagnosis of tricuspid atresia was made in all but the first case here reported by correlating the infants' cyanosis and evidence of left ventricular enlargement as shown by fluoroscopy and the electrocardiogram. The murmurs and thrill, if present, are of little value in differential diagnosis. Cardiac catheterization may provide a further useful study.

Among the total of thirty-seven patients available, thirteen were male and sixteen female. There were two Negro infants. Cyanosis was reported present in thirty patients, dyspnea in eleven, cough in three, and convulsions in two. Six patients had polycythemia, and five had clubbed digits. Fourteen died before the sixth month and fourteen between the sixth and twelfth months. Three died in the second year, and six lived from two and one-half to five years. Barring incidental disease, life was prolonged in patients having relatively large or multiple interauricular and interventricular septal defects. Closure of the foramen ovale and ductus arteriosus proceeded normally in these infants, despite the resulting damage to the whole body with a shortening of life. This suggests that these structures naturally degenerate and disappear after three to twelve months of postnatal life.

The cyanosis found is due to subnormal oxygenation of the systemic circulating blood, since the lungs receive only the small amount of blood that can pass through the interventricular septal defect, the bronchial arteries, and the ductus arteriosus, if patent. Abnormal intracardiac shunts account for the murmurs and thrills. As the left ventricle must move at each systole all the blood that the heart receives, it becomes dilated, hypertrophied, and subsequently fails. The right ventricle is merely a passageway for the small blood current from the interventricular septal defect. The disproportion in size of the two ventricles explains the electrocardiographic left axis deviation.

Four reported patients died with complicating bacterial endocarditis, and in four others there was cerebral thrombosis, hemorrhage, or abscess. Most of the other deaths appeared attributable to congestive heart failure and anoxia.

THERAPY

More than two-thirds of the patients in the cases reviewed died before completing the first year of life. In four instances, surgical vascular shunts of the Blalock or Potts type were made without a striking increase in longevity. In this

group those with the largest interauricular and interventricular shunts tended to survive longest. Also, tricuspid atresia associated with transposition of the great vessels may have a better prognosis, i. e., up to 56 years of life.[43]

In a consideration of possible surgical treatments of the condition, enlarging the interauricular septal defect and producing a ductuslike defect between the aorta and pulmonary artery would seem most practicable. Perforation of the atretic right atrioventricular septum would be technically difficult, and it is questionable how much increase in blood flow the underdeveloped right ventricle could accommodate.

DISCUSSION

It appears that tricuspid atresia is not so rare as previously supposed. As more surgical procedures are done in congenital heart disease, the incidence will no doubt rise. The diagnosis can be made relatively easily, for in practically no other congenital cardiac anomaly do cyanosis and electrocardiographic evidence of left ventricular preponderance occur together in infancy.

As to the origin of tricuspid atresia, emphasis has previously been placed on the anomalous fusion of septa or endocardial cushions as the primary event. Little attention has been paid to the presence or absence of anomalies of the superior vena cava or right atrial cavity which might divert the blood flow away from the atrial floor and through the foramen ovale. Tricuspid atresia with its associated findings is usually an isolated major anomaly which can be satisfactorily explained by the mechanical effects of abnormal blood flow currents in the primitive right atrium.

If such patients are to be aided significantly by any surgical procedure, it is evident that a more radical approach will be necessary. Not one but two operations may be required: first, creation of a widely patent interauricular septal defect and, second, creation of a shunt from the systemic to the pulmonary arterial circulation.

SUMMARY

Six fatal cases of primary isolated tricuspid atresia in infants have been described, and thirty-one acceptable similar cases have been collected from the literature. An abnormal superior vena cava, a right atrial Chiari's network, or both were found in the six new patients. The characteristic clinical findings of cyanosis and electrocardiographic left axis deviation aid in the diagnosis. Most patients die before 1 year of age because of congestive heart failure and anoxia.

Tricuspid atresia may be satisfactorily explained mechanically by the presence of abnormal blood currents in the primitive right atrium which allow the tricuspid ostium to close. To prolong life, surgical enlargement of the associated interauricular septal defect and creation of a systemic-to-pulmonary arterial shunt are proposed.

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Clinical Reports

RHEUMATIC HEART DISEASE WITH MASSIVE THROMBOSIS OF THE LEFT AURICLE

ANTON S. YUSKIS, M.D.

SAN DIEGO, CALIF.

THROMBOSIS of the left auricle is very rare, and reports in the literature are few. The French writers have published excellent articles, but no reports were found by American or British writers. Ball thrombus of the left auricle, on the other hand, has been well described by American writers. Rheumatic heart disease with thrombosis and canalization of the left auricle is therefore an apparent rarity.

CASE REPORT

A white man, aged 48 years, was first seen on Oct. 5, 1948, complaining of dyspnea, weakness, and cough. He had been in fairly good health until one year before, when he developed bouts of paroxysmal dyspnea. One month before, he developed an upper respiratory infection that was followed by weakness, cough with blood-tinged sputum, fever, and dyspnea. The systemic inventory and the family history were noncontributory. The past medical history revealed that he had had "acute inflammatory rheumatism" at the age of 10 years in Scotland, and following this illness he was told that he had a heart murmur.

Physical examination revealed an acutely ill, poorly nourished, nervous, irritable, orthopneic white man. The temperature was 101.6° F. with an irregular pulse rate of 120 per minute and a blood pressure of 110/80 mm. Hg and 114/82 mm. Hg in the right and left arms, respectively. The pharynx was normal. There was a moderate hydrothorax of the right pleura. In the left lung there were coarse basal râles. The heart showed Grade 3 cardiac enlargement. There was an accentuated thrust over the pulmonic area. P_2 and M_1 were loud and snapping, and there was a loud apical systolic murmur transmitted to the left axilla. The rest of the physical examination was normal.

His first hospital admission was for a period of three weeks. At this time the hemoglobin was 16 Gm., red blood cells 4,800,000, white blood cells 23,300 with 86 per cent polymorphonuclear leucocytes, of which 76 per cent were segmented, 10 per cent stab forms, and 14 per cent lymphocytes. The blood Wassermann was negative, and the sedimentation rate was 25 mm. (Cutler). The urinalysis showed a 2 plus albuminuria. An electrocardiogram (Fig. 1), which consisted of the standard limb leads, six unipolar precordial leads, and the augmented unipolar limb leads of Goldberger, showed auricular fibrillation, digitalis effect, and myocardial anoxia. A roentgenogram of the chest (Fig. 2), taken after 2,000 c.c. of blood-tinged fluid were removed from the right chest, showed a right pneumohydrothorax, hilar vascular markings, diffuse, hazy, and of the central radiating type, generalized cardiac enlargement, and a very prominent right cardiac border. The aortic knob was absent, and the left cardiac border was straight with convexity of the pulmonary conus. The patient was too sick for a fluoroscopic examination.

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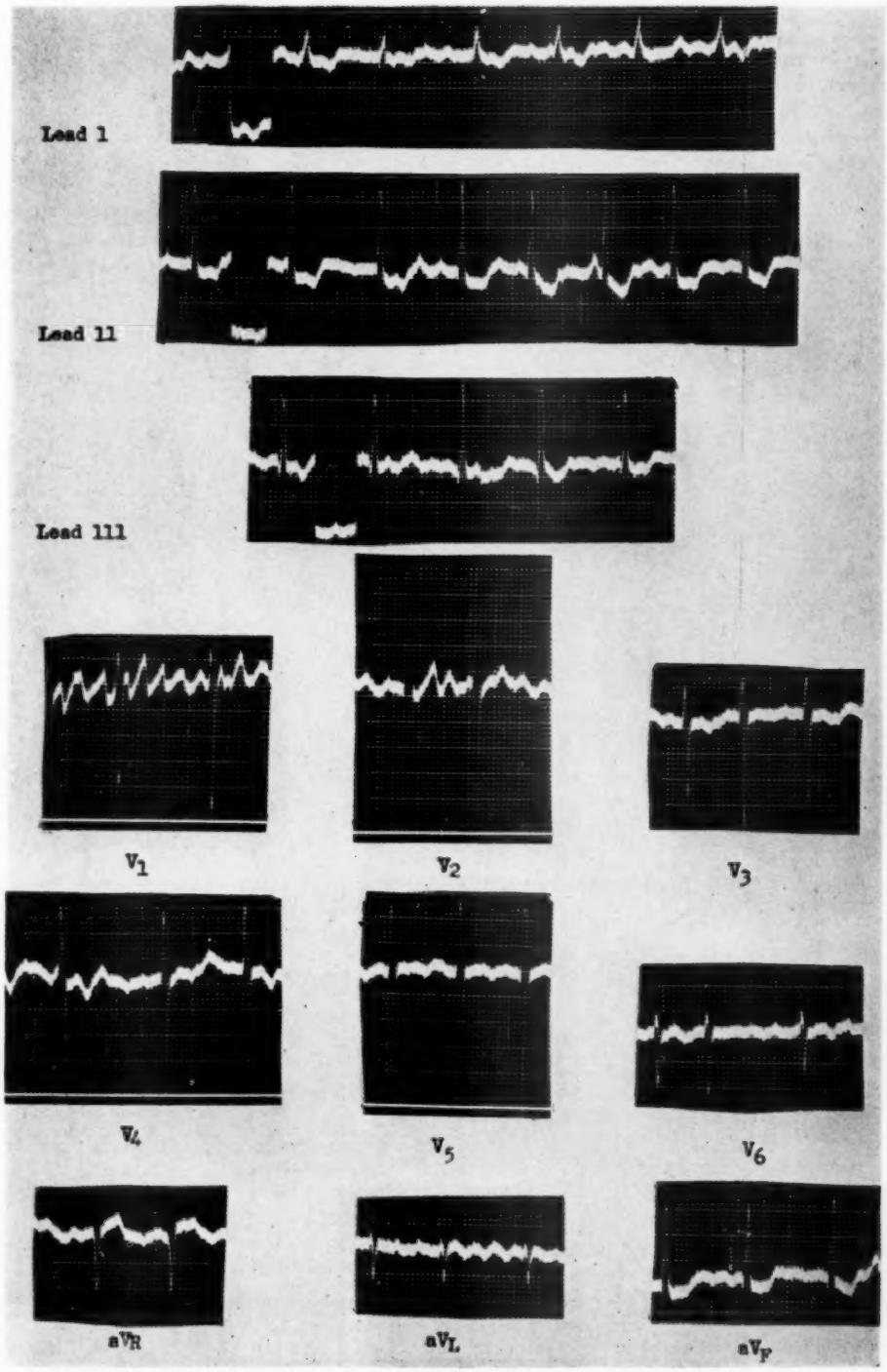

Fig. 1.—Electrocardiogram showing auricular fibrillation, digitalis effect, and myocardial anoxia.

The patient had a very stormy course; the temperature ranged from 99° to 102.6° F., the apical heart rate from 100 to 148 with attacks of severe orthopnea. A sensation of tightness and constriction was present under the sternum. Motion or change of position would produce dyspnea and palpitation. It was felt that the patient had active rheumatic fever with rheumatic pneumonitis in addition to his mitral insufficiency and possible mitral stenosis.

He continued to improve and went home on Oct. 26, 1948. It seemed that in the next two months he might recover, but during this time an aortic diastolic murmur appeared.

On Dec. 29, 1948, the patient had a sudden rise in temperature to 101° F., associated with marked dyspnea and weakness. A few râles were heard in the right base. His condition became gradually worse, and he was admitted to the hospital again on Jan. 17, 1949. He ran a febrile course with many râles and fluid in the left pleura, developed acute right heart failure, and died on Jan. 20, 1949.

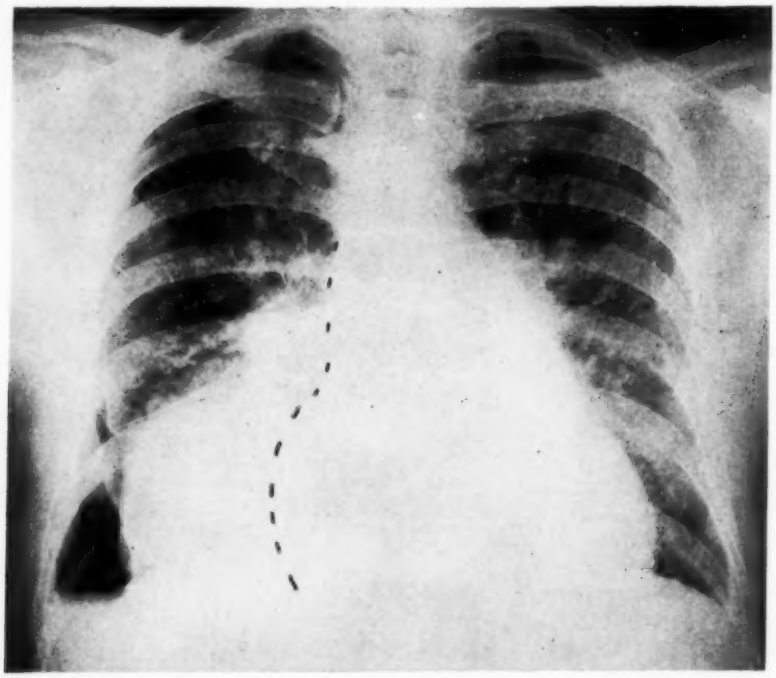

Fig. 2.—Roentgenogram of chest showing right hydropneumothorax, hilar vascular markings, and generalized cardiac enlargement with a prominent right cardiac border and the straight convex left cardiac border.

An autopsy disclosed a large heart weighing 545 grams. The right auricle was large and dilated. The right ventricle was hypertrophied, measuring 10 mm. in thickness. The left auricle was enormously dilated and extended posteriorly and to the right (Fig. 3). The left auricular cavity was almost entirely occupied by a massive organized thrombus measuring approximately 6 cm. in diameter, the center of which was bright yellow and partially liquified. There was a narrow pencillike channel along the posterior surface of the left auricle behind the thrombus. The thrombus extended down onto the mitral valve which was extremely stenotic and fibrous. The left ventricle was normal. Histological sections showed rheumatic endocarditis, rheumatic myocarditis, and rheumatic arteritis.

The pleura over the right lung was thickened to 3 mm. The entire right lung was diffusely involved by a patchy consolidation. Multiple sections through the right lower lobe revealed a triangular-shaped cavity lined with a dense fibrous wall measuring 3 by 2 by 2 cm. Careful dissection of the adjacent pulmonary artery disclosed an old, organized degenerating infarct.

The left lower lobe was dry, granular, and fleshy. The walls of the pulmonary artery were thickened. Microscopic sections showed pulmonary atherosclerosis, chronic passive congestion, chronic rheumatic pleuritis, and rheumatic pneumonitis.

COMMENT

An extensive literature exists on thrombosis and rheumatic heart disease, but no detailed reports on massive or extensive auricular thrombosis with or without canalization could be found except in the French literature, where Soulie and associates[1] reported three cases.

Fig. 3.—Photograph showing the opened left auricle and left ventricle. The auricular thrombus is adherent to the walls, extends on and into the stenosed mitral orifice (pointer), and is composed of layers.

Graef and co-workers[2] have shown that intracardiac thrombosis is a relatively uncommon event in rheumatic heart disease. They found that active rheumatic auricular endocarditis plays an important role in left auricular thrombosis as obtained from histological observations, while right auricle thrombus formation is related to disturbances in hemodynamics. They found that, when

the factors of congestive heart failure and active carditis were controlled, active auricular endocarditis appeared in 47 per cent of the cases of rheumatic heart disease with auricular thrombosis in contrast to its appearance in 24 per cent of the cases of a similar group without thrombosis and that the incidence of auricular fibrillation and the degree of mitral stenosis in both groups were practically the same. In patients who died of rheumatic heart disease in congestive failure, active auricular endocarditis was observed twice as frequently in those with auricular thrombosis as in those without this, although the incidence of auricular fibrillation and the degree of mitral stenosis were about the same in both groups. They concluded that certain conditions favor the development of auricular thrombi, namely, severe mitral stenosis together with congestive heart failure, auricular fibrillation, and the persistence of active rheumatic fever.

The outstanding clinical picture presented by this case was the severe acute rheumatic carditis. The most important symptoms were dyspnea and orthopnea, which were very prominent and severe. There were no clues to suspect a cardiac thrombus as there was no transient or permanent interference with the peripheral circulation. Active rheumatic fever was demonstrated by the aortic endocarditis, myocarditis, pneumonitis, and pleuritis. Due to thrombosis of the left auricle, the diastolic murmur of mitral stenosis could not be heard, though it was suspected and searched for during every examination of the heart.

SUMMARY

A case of massive thrombosis with canalization of the left auricle in chronic rheumatic valvular disease with active rheumatic fever is reported.

The author wishes especially to thank Dr. George C. Griffith for his guidance and help in this report, and also Drs. Robbins, F. E. Jacobs, and De Santos for their help.

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ANEURYSM OF A SINUS OF VALSALVA WITH RUPTURE INTO THE RIGHT AURICLE

ISAAC A. KAWASAKI, M.D.,* AND F. BERNARD SCHULTZ, M.D.**

HONOLULU, HAWAII

IN THE very few described cases of this rare condition, most instances of death were preceded by congestive heart failure. In searching the literature it has been found that aneurysm of a sinus of Valsalva with rupture into the right auricle has been reported on exceptionally few occasions. However, aneurysm in the sinus of Valsalva with rupture into the right ventricle has been reported numerous times, and these are listed by Taussig.[1] In 1919, Abbott[2] reported the study of a case of ruptured aneurysm of a sinus of Valsalva into the right auricle. In 1928, Laederich and Poumeau-Delille[3] reported the next case. In 1937, Wright[4] collected three cases in the then current literature other than those above and mentioned a fourth case. In May, 1945, one of us (I.A.K.), in collaboration with Benenson,[5] reported a case in an apparently well soldier who died within a few minutes of his first complaint. Recently a patient who had an admission diagnosis of acute endocarditis was brought to the attention of the writer (F.B.S.). Certain unique features were brought out in this case which are interesting, as well as the autopsy findings of rupture of an aneurysm of a sinus of Valsalva into the right auricle.

CASE REPORT

A 52-year-old Filipino laborer was admitted to the hospital on private service with complaints of fever, weakness, and some difficulty in breathing. Through an interpreter it was learned that he had been sick for more than a week with what he thought was a bad cold. He continued his daily work with self-medication. However, his condition became worse, and he was taken to a doctor by a friend. At this time his chief complaint was weakness and inability to walk. Following his visit to the doctor he rested at home a few days and developed a "bad pain in his chest, the upper part of his back, and neck." At this time he was hospitalized.

On admission the patient was found to be a fairly well-developed and nourished Filipino, feverish, but not acutely ill. There was no evidence of dyspnea or cyanosis. The blood pressure was 88 mm. Hg systolic and 30 mm. Hg diastolic. The skin was moist; there was no rash and no adenopathy. The head and neck were negative with no engorged veins. The lungs were clear, and the breath sounds were normal. The heart did not appear enlarged on percussion. At the time of admission, one observer thought he heard a soft systolic murmur at the apex as well as a systolic murmur at the aortic region. The abdomen was soft and no tenderness was elicited; neither were there any masses felt. The genitalia were negative as were the extremities. There was no clubbing of the fingers. The reflexes were within normal limits, and there was no Babinski. The temperature was 103° F., pulse 96 per minute with normal sinus rhythm. The respirations were 36. His chief complaints at this time were head and back pains, vague in character and not localized. Tables I, II, and III give the laboratory data from admission to death.

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*Pathologist, Kuakini Hospital, Honolulu.

**Chief of the Cardiac Clinic and Heart Station, Kuakini Hospital, Honolulu.

TABLE I. BLOOD COUNTS

	HEMOGLOBIN	RBC	WBC	POLYMORPHONUCLEARS	SMALL MONONUCLEAR LEUCOCYTES
March 29, 1947	98.6% (15.1 Gm.)	4.9 mil.	14,650	95	5
April 1, 1947	87.1% (13.6 Gm.)	4.0 mil.	18,000	82	18
April 3, 1947	89.7% (13.9 Gm.)	4.0 mil.	17,200	79	21
April 7, 1947	94.6% (14.7 Gm.)	4.2 mil.	14,200	77	23

TABLE II. BLOOD CHEMISTRY

	NONPROTEIN NITROGEN	SUGAR	BLOOD PROTEINS
April 3, 1947	28.6	126	5.35%
April 7, 1947			5.56%
April 14, 1947	93.6		5.04%

TABLE III. URINALYSIS

	SUGAR	REACTION	SPECIFIC GRAVITY	ACETONE	ALBUMIN
April 2, 1947	6 Gtt. 4 +	acid	1.020	negative	negative
April 3, 1947	6 Gtt. 4 +	acid	1.020	negative	negative
April 7, 1947	6 Gtt. 4 +	acid	1.038	negative	trace

April 2, 1947, there were occasional epithelial cells and a few leucocytes, together with a few hyaline casts and mucous threads noted microscopically.

Blood cultures on March 29, 1947, showed one colony of *Staphylococcus albus*. Four days later, another blood culture was reported negative. As the clinical picture was regarded as a bacterial endocarditis, penicillin was started, the patient receiving 100,000 units every two hours. The patient did fairly well until the third hospital day, except that he did not respond readily and seemed slightly disorientated. On the third hospital day, there was excessive diaphoresis which continued throughout his hospital stay. This was followed by a severe chill which lasted approximately twenty minutes. Following the chill, the patient again began to respond to treatment and seemed to feel better and became afebrile. On the sixth hospital day, an electrocardiogram was taken (Fig. 1) and was interpreted as follows: ventricular rate 107; QRS interval 0.06 second; absence of P waves in all leads. There was a slight depression of the ST segment in Leads I, II, and III, with a marked elevation of the ST segment in CF_4 and inversion of T. The interpretation was auricular tachycardia with anterior septal damage.

A chest plate (Fig. 2) was read as follows: "Heart appears somewhat enlarged to the left. Extensive pulmonary infiltration; there is a fairly homogeneous opacity occupying the entire left lung with the exception of the apex and a small aerated portion of the lung in the base. There are rather fibrous appearing infiltrations in the upper lobe of the right lung. The middle lobe fissure is displaced superiorly. Similar but less extensive infiltrations are noted in the lower medial portion of the lung. The nature of these changes is unknown. From the fact that the middle lobe fissure is displaced upward, the infiltrations in the upper right lobe have probably been present for some time and a pulmonary tuberculosis must be considered in this region. The character of

the opacity in the left lung is different and suggests more of a pneumonic process. Because of the cardiac enlargement there is also a possibility that some of the pulmonary changes may be on the basis of cardiac decompensation."

On the thirteenth hospital day the patient coughed up bloody sputum, which was negative for tubercle bacilli. The patient had been digitalized and penicillin was being continued. However, the patient became restless and had to be continually watched. This was followed by incontinence, and he gradually went down hill. On the seventeenth hospital day the patient died.

Autopsy Findings.—An autopsy was performed seven and a half hours following death. The body was that of a well-nourished Filipino male about 50 years of age. There were no deformities, wounds, fractures, or scars. There was moderately severe pitting edema present on the back and sacral area. Rigor mortis was moderately pronounced throughout the body. Post-mortem

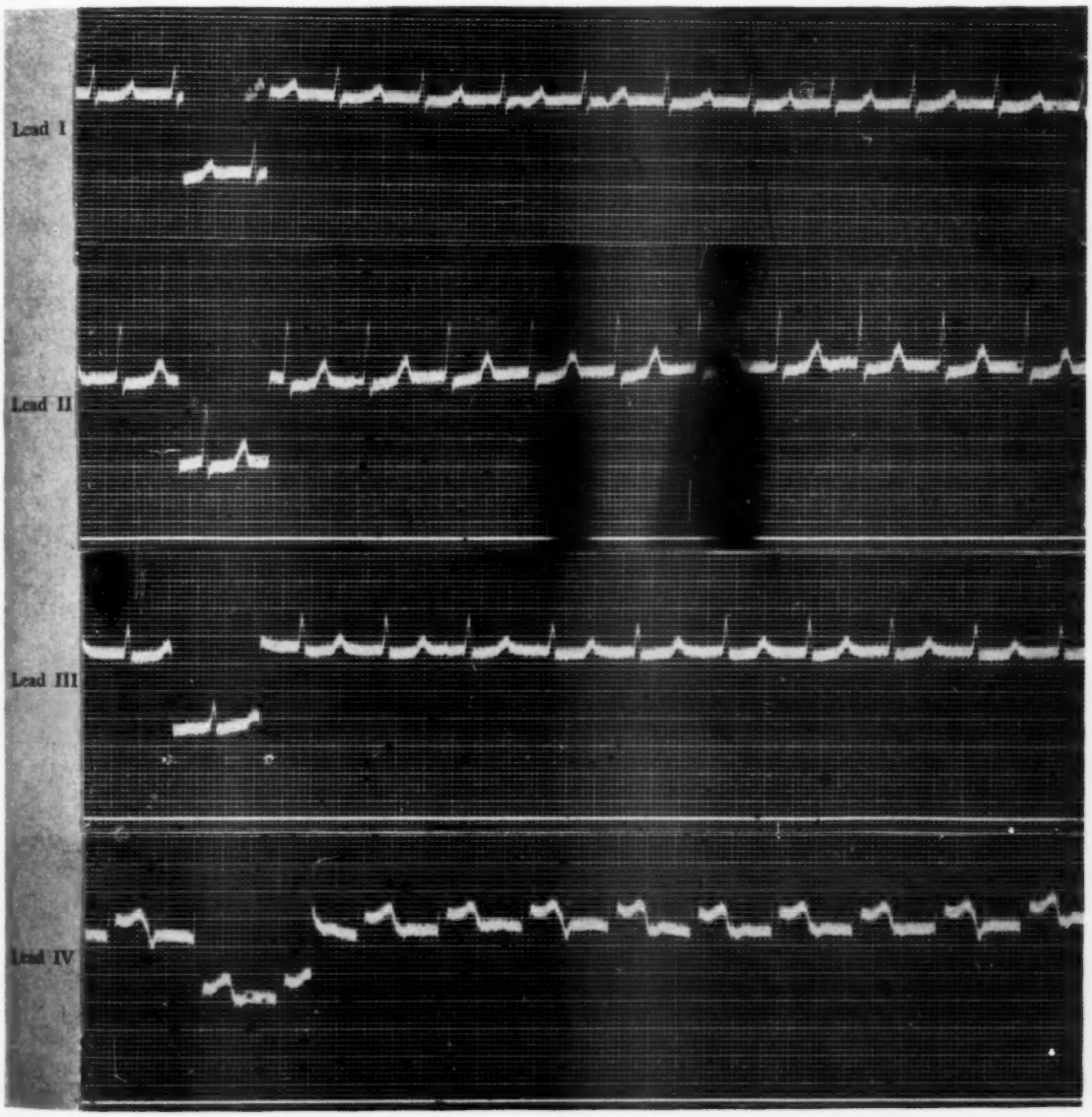

Fig. 1.

lividity was present over the back, neck, and lower limbs. The superficial lymph nodes were not palpable. The pupils were round and equal, measuring 6 mm. in diameter. There were no discharges from the ears, nose, or mouth. The gums and teeth were not significant.

The breast plate was removed with ease, revealing dense fibrous adhesions over the entire left pleural sac and moderate fibrous adhesions over the right sac. The right pleura contained about 50 c.c. of clear straw-colored fluid. The pericardium having been opened, the lining serosa showed nothing of note. The organs in situ in the thorax were in the usual relations. The diaphragm was at the level of the fourth interspace on the right and the sixth rib on the left.

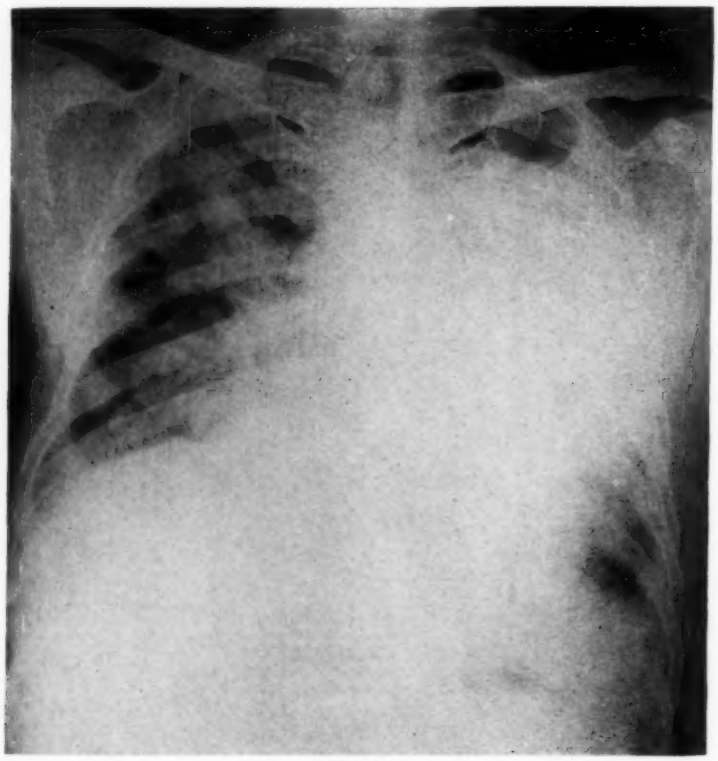

Fig. 2.

The heart weighed 325 grams. The organ was somewhat flabby, dilated and the cardiac chambers being opened, an ulcerative and vegetative area of the right posterior segment of the aortic semilunar valve was found. This ulceration was so severe that the valve flap was broken down. There was a perforation (Figs. 3 and 4) at the base of the sinus of Valsalva extending through the interventricular septum and forming a large pedicle of fibrin and blood clot covered with endocardial lining within the right chamber protruding above the tricuspid valve leaflet. The perforation extended at the base of this protruding pedunculated mass and showed a free communication between the right and left side of the heart. The pedunculated mass in the right chamber measured 2.5 cm. in long diameter, was irregularly clubshaped, and smooth surfaced. The vegetation appeared dark-reddish in color, as compared to the pallor in the left chamber, and involved the aortic valve leaflet where the vegetation was more fibrous in character. The remaining valve leaflets were free from any destructive process. Sections into the heart muscle showed a moderate degree of pallor throughout with marked swelling of the muscle fibrous bundles. There was a general sprinkling of atheromatous plaques in the coronary vessels, but few atheromatous plaques were seen in the aortic intima except at the border of the destroyed semilunar valve.

The aorta and branches showed generous sprinkling of atheromatous plaques, but no ulceration or calcification was seen.

The right lung weighed 895 grams and the left 790 grams. The left lung showed torn surfaces due to the dense fibrous adhesions. Upon section, there were discrete areas of marked congestion not unlike multiple infarcts. Both lung bases showed heaviness with increased fluid content and blood. In the right lung there were also small areas of consolidation which appeared reddish in color. Some, however, near the main stem bronchi appeared to be gray consolidation of pneumonitis. The bronchial tree showed marked congestive changes with purulent exudate. The hilar nodes were generally swollen.

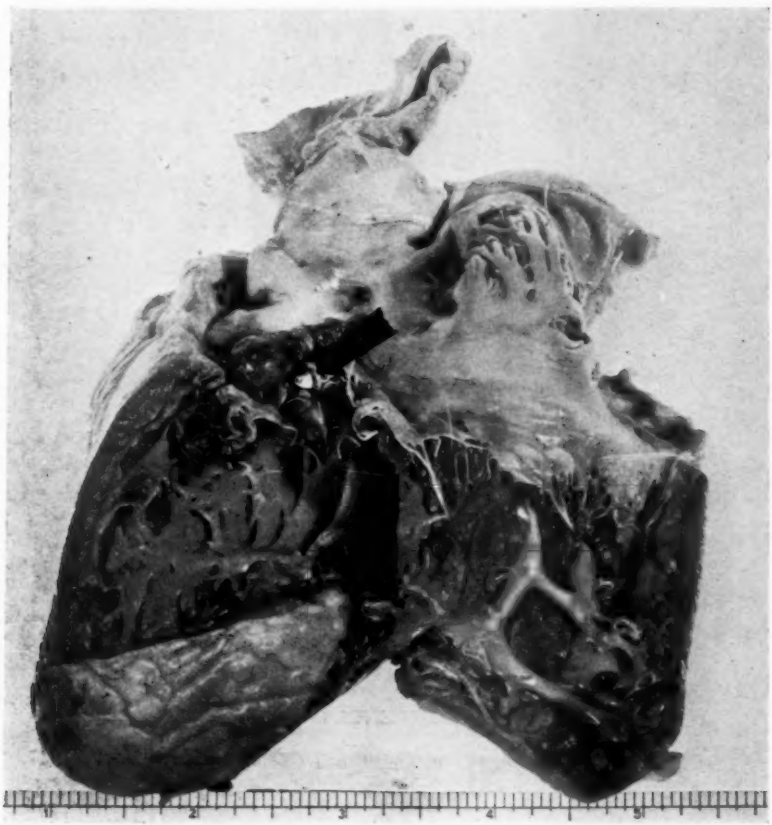

Fig. 3.

DISCUSSION

Aneurysms of the sinus of Valsalva have been reported quite rarely, more rarely in those cases where rupture has perforated into the right auricle. In most instances, death resulted after a period of congestive heart failure. The exact mechanism of death is conjecturable. There is anatomical evidence of dilatation of the right side of the heart and of myocardial ischemia. A perforated aneurysm constitutes a massive arteriovenous fistula with sudden onset. The aneurysm in this case was filled with blood clot, and only the base was perforated. This, in addition to the valvular endocarditis, would result in changes in the

circulatory dynamics of the coronary vessels. The patient may have expired from coronary insufficiency from the above lesions and cardiac failure.

SUMMARY

A case of rupture of an aneurysm of the sinus of Valsalva into the right auricle is reported. This lesion is probably secondary to damage of the area by bacterial endocarditis.

Fig. 4.

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EXTRAORDINARY ALTERATION OF THE P-R INTERVAL IN NEUROCIRCULATORY ASTHENIA

The Role of Emotional Influences

Jacob J. Silverman, M.D., and Rowland D. Goodman II, M.D.

Staten Island, N. Y.

THE P-R interval, a measure of auriculoventricular conduction, varies with body size and heart rate, and in normal adults seldom exceeds 0.21 second. Auriculoventricular block of slight degree is relatively common in electrocardiographic practice. However, the higher degree of impaired auriculoventricular conduction time, those exceeding 0.50 second, is decidedly rare. As Faulkner[1] pointed out, the extreme grades of auriculoventricular block are rarely encountered because of two limiting factors: In the first place, as the P-R interval increases in length, the refractory period of the auriculoventricular node also tends to become prolonged, and when a critical lengthening is reached, the auriculoventricular node is completely refractory. In this way dropped beats are formed. Second, if the supraventricular pacemaker is unusually delayed, the inherent ventricular pacemaker may take over to initiate escaped beats.

We have recently encountered a delay in auriculoventricular conduction time that is unusual and interesting for two reasons. In the first place, the patient demonstrated a P-R interval of 0.72 second. This is one of the longest P-R intervals on record. Thayer,[2] in 1915, using polygraphic tracings, reported a patient who demonstrated an A-C interval amounting to 0.70 to 1.0 second. Ashman and Hull[3] noted a P-R interval of 1.01 second. Faulkner[1] reported an extraordinary degree of heart block in which the P-R interval measured 0.80 second and actually exceeded the R-R interval. Our case is of additional interest in that the extraordinary P-R interval of 0.72 second was labile and seemed to vary with the emotional status of the patient. When the patient was first studied he was in an anxious state, and at that time the P-R interval was unusually prolonged. With relaxation and without drugs, his P-R interval spontaneously shortened to 0.32 second. Daily electrocardiograms were taken, all in the recumbent position, and remarkable fluctuations in the P-R interval were observed. As far as we were able to determine, the only reason for the spontaneous changes in the P-R interval was the improvement or deterioration in the emotional status of the patient.

CASE REPORT

The patient was a 49-year-old army sergeant with over twenty-five years of active military service. His chief complaint was nervousness, and on close questioning he admitted a multitude

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of complaints, such as palpitation, weakness, easy fatigability, and insomnia. He found it increasingly difficult to concentrate on his jobs, which, incidentally, were of a light nature. He was a heavy smoker. There was no history of rheumatic fever. In October, 1935, he was studied at the Walter Reed General Hospital for "stomach" complaints, and at that time, because of a basal metabolism reading of −13 per cent, he was considered to have mild hypothyroidism. He was placed on thyroid extract and returned to duty one month later as improved. In March, 1939, he complained of vague abdominal pains and nervousness and was again studied at the Walter Reed General Hospital. During a routine medical survey an electrocardiogram was taken, and this disclosed a prolonged auriculoventricular conduction time, varying from 0.28 to 0.32 second. Cardiac examination, however, was considered normal, and fluoroscopic study of the heart disclosed no abnormalities. He was returned to duty without any medication. In the intervening six years he carried on satisfactorily except for episodes of nervousness.

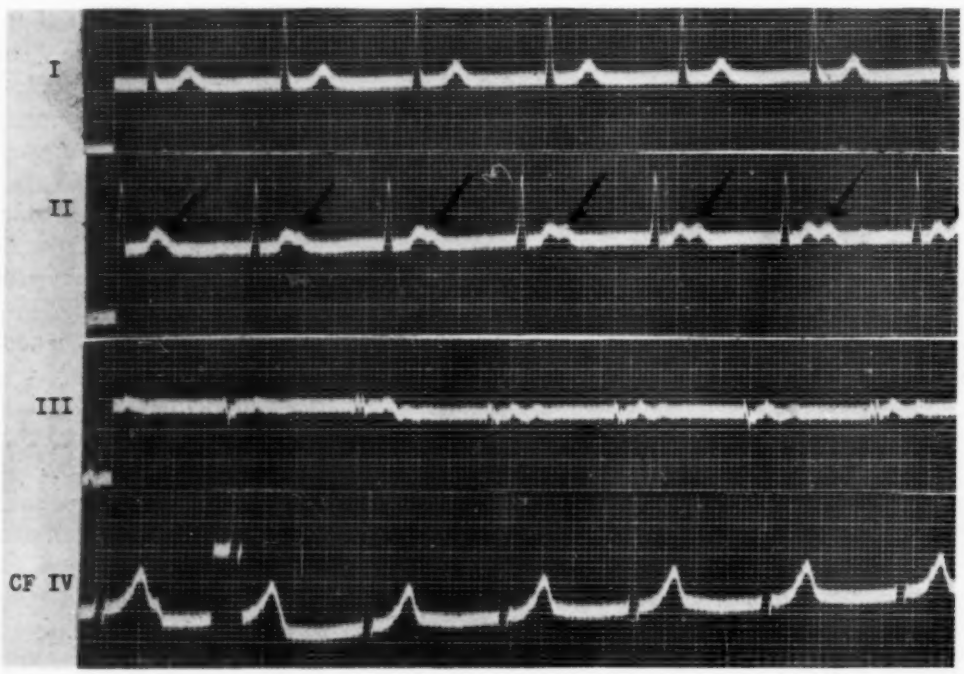

Fig. 1.—Electrocardiogram demonstrating a P-R interval of 0.72 second. The T waves in Lead II are indicated by the arrows. The P waves in Leads I and CF_4 are incorporated in the T waves (see Fig. 2).

When he came under our observation in April, 1945, examination disclosed an anxious, middle-aged soldier with good development and a tendency toward obesity. His palms were excessively moist, and there was a tremor of large amplitude to the outstretched fingers. He was afebrile. The thyroid gland was not enlarged; there was no exophthalmus. The reflexes were hyperactive. On examination the heart was considered normal except for a Grade 2 systolic murmur over the apex. The blood pressure measured 130 mm. Hg systolic and 76 mm. Hg diastolic. The pulse was regular and averaged 72 per minute. Ophthalmoscopic examination disclosed no abnormalities. An exercise tolerance test gave a normal response, as demonstrated by a prompt return of pulse and blood pressure to normal levels. Routine laboratory studies, such as urinalyses, blood counts, sedimentation tests, serology tests for syphilis, blood cholesterol, and blood nonprotein nitrogen determinations were within normal limits. A fluoroscopic study

of the chest disclosed a transverse type of heart with questionable slight left ventricular enlargement. There was no evidence of auricular enlargement. The important positive findings were limited to the electrocardiographic studies. Fig. 1 demonstrates an electrocardiogram taken on the day of admission. This tracing shows a P-R interval of 0.72 second, indicating an incomplete auriculoventricular block. The T waves in Lead II are indicated by arrows; the P waves in Leads I and CF_4 are incorporated in the T waves. Subsequent electrocardiograms were taken during the patient's stay in the hospital, and daily fluctuations in the P-R interval were noted. When the

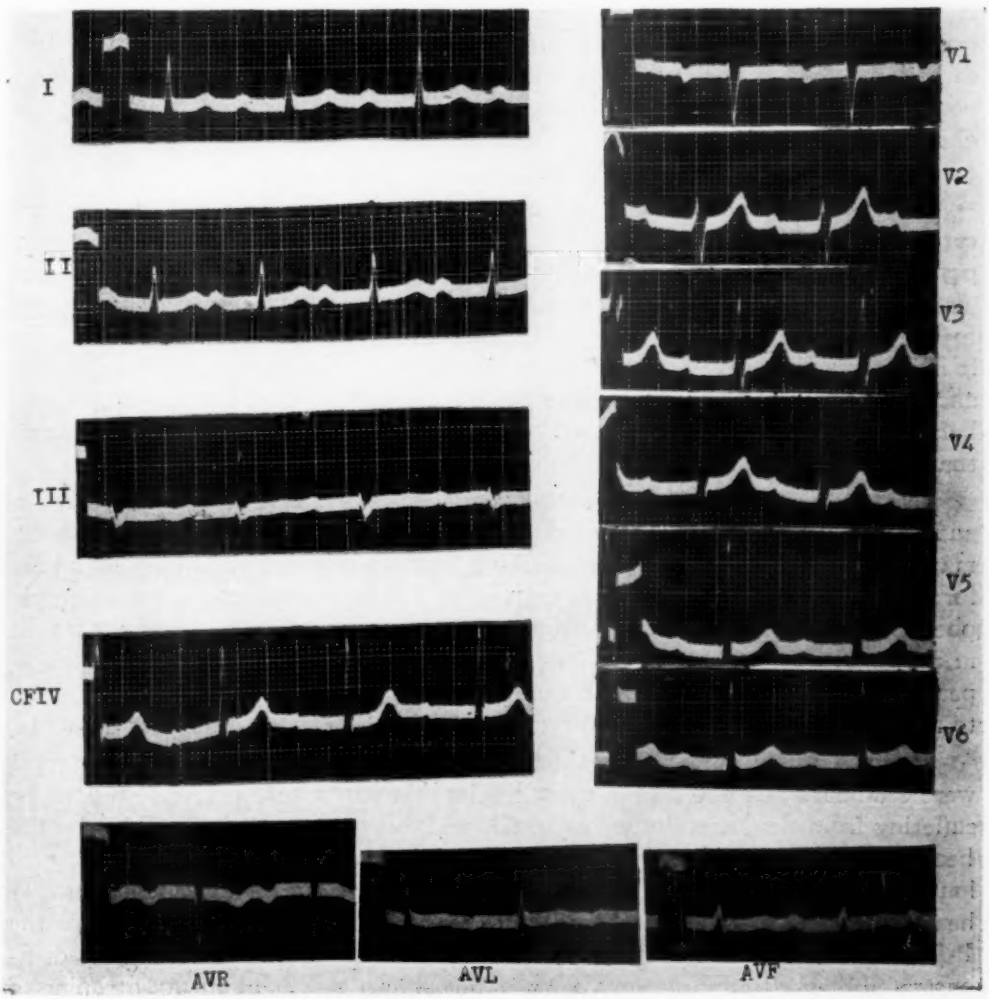

Fig. 2.—Electrocardiogram taken when the patient was relaxed. The P-R interval now measures 0.32 second.

patient was relaxed and comfortable, the P-R interval was reduced to 0.32 second (Fig. 2). A Master's two-step exercise test was performed when the patient was relaxed, but no significant changes in the P-R interval, RS-T segment, or T waves were observed. Unipolar, precordial, and extremity studies were normal except for the prolonged P-R interval. A diagnosis of incomplete auriculoventricular block of undetermined etiology was made. The patient was eventually retired from the army on a psychiatric basis.

DISCUSSION

In interpreting a prolonged P-R interval it is important to recognize that not all prolongations are due to extrinsic heart disease. Occasionally, a prolonged P-R interval is found in normal individuals or in persons without any structural heart disease. Graybiel and his co-workers[4] examined the electrocardiograms of 1000 young, healthy aviators and found that a prolongation of the P-R interval was present in sixteen. According to White,[5] the more common type of prolongation of the P-R interval is temporary and functional and is caused by a wide variety of conditions, such as excessive vagal stimulation, postural and respiratory influences, asphyxia, drug poisoning (digitalis and quinidine), vegetable and mineral poisons, uremia, and certain infectious diseases, such as rheumatic fever, diphtheria, and viral diseases.

There have been an increasing number of reports dealing with the electrocardiographic changes in subjects with neurocirculatory asthenia and other psychoneuroses.[6-10] Cardiac arrhythmias may be precipitated by emotional disturbances, but the most frequent changes observed have been those confined to the T wave of the electrocardiogram.[11] In studying emotional influences it is important to take frequent electrocardiograms during the psychic disturbance rather than at random. Mainzer and Krause,[12] in a careful study of patients before, during, and after the anxiety associated with surgical procedures, found that 40 per cent demonstrated definite electrocardiographic abnormalities.

Neurocirculatory asthenia, classified under many headings, is basically an anxiety state.[13] In this disorder there are all kinds of excessive vagosympathetic manifestations. One of the most striking findings in neurocirculatory asthenia, for example, is excessive palmar sweating.[14-15] Palmar sweating is a cholinergic phenomenon and is abolished by atropine. Cholinergic influences causing changes in the heart are well known. Conduction between the auricle and ventricle is peculiarly sensitive to vagal influences. It should not be surprising, therefore, to find alterations of the P-R interval in patients with neurocirculatory asthenia.

In an Army hospital during the last war, 100 cases of prolonged P-R interval were studied by Logue and Hanson.[17] In this study seven were found to be suffering from neurocirculatory asthenia, and nineteen were classified under the heading of "no disease." In the remaining seventy-four patients with a prolonged P-R interval, evidence of disease was found, but it was not necessarily heart disease. In one patient without evidence of any organic disease, the P-R interval measured as much as 0.40 second. Many of these patients demonstrated marked variation of vagal tone as shown by the ability of atropine to shorten the P-R interval. The observation that atropine shortens the prolonged P-R interval in the patients with rheumatic fever, as well as vagotonic individuals, first observed by Bruenn[18] in 1937 and subsequently confirmed by others,[19-21] has led to the concept that impairment of the auricular conduction time is in some way related to increase in vagal tone. Experimentally, Robinson and Draper[22] demonstrated marked changes in auricular conduction time in a normal individual by stimulating the vagus nerve. Similarly, Sigler[23] reported pronounced vagal defects, producing various grades of auriculoventricular block

by means of carotid sinus pressure. Weiss and Ferris[24] described two patients with Stokes-Adams syndrome with complete block of vasovagal origin associated with the act of swallowing; both were relieved by atropine. Poel,[25] in 1942, reviewed three cases and reported in detail a case of functional heart block due to vagal effect.

In our patient the pronounced prolongation of the P-R interval was interpreted at first as indicating myocardial damage, such as occurs in rheumatic fever, and as the P-R interval shortened, improvement in the cardiac status was considered to take place. When it was noted, however, that the P-R interval shifted in an amazing way back and forth, unrelated to other clinical changes, this interpretation was questioned. The patient was afebrile, and at no time were there changes in the erythrocytic sedimentation determinations. Exercise tolerance studies remained unchanged. Unfortunately, conditions prevented us from carrying on pharmacologic studies as reported by Wendkos.[26] Nevertheless, the patient was carefully observed by the same examiners over a period of several months. On clinical grounds the examiners were convinced that the P-R fluctuations were benign and related to the patient's emotional status. The unusually prolonged P-R interval was noted only when he was tense and anxious. On these occasions he demonstrated an excessive palmar sweat response and a tremor of large amplitude. As shown elsewhere,[27] this combination of excessive palmar sweating and pronounced tremor is a striking feature of neurocirculatory asthenia and occurs almost exclusively in patients suffering from an anxiety state. When our patient was calm, his palms became dry and his tremor subsided. It was at this time that the P-R interval was markedly shortened. It seemed that our patient, when he was relaxed, was able to counteract excessive vagal activity by some unknown mechanism similar to the action of atropine.

SUMMARY

1. Extraordinary alteration in a P-R interval measuring 0.72 second is recorded in a patient with neurocirculatory asthenia.

2. Conduction between auricle and ventricle is sensitive to vagal influences and may be modified at times by the emotions.

3. In interpreting changes in an electrocardiogram, the emotional status of the patient should be considered.

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